Clinical and haematological aspects of cerebral venous thrombosis

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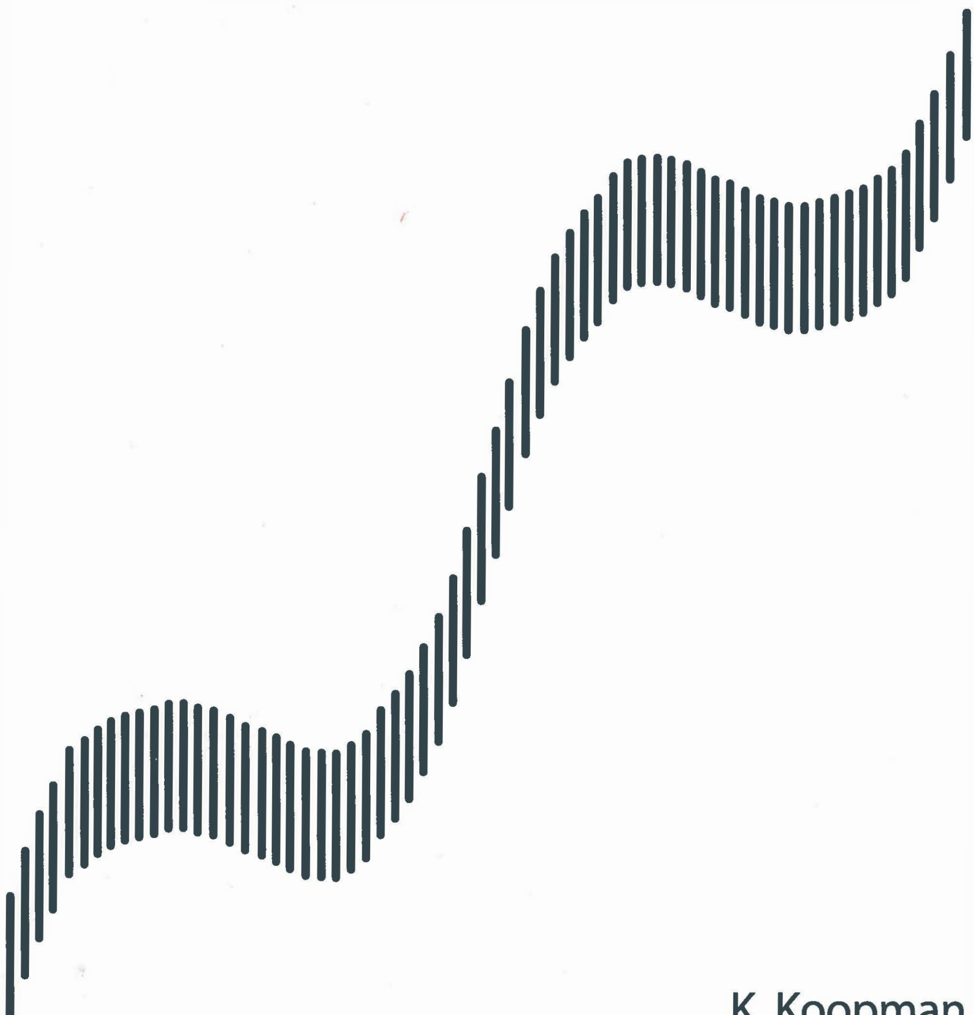

K. Koopman

Clinical and haematological aspects of cerebral venous thrombosis

Stellingen behorende bij het proefschrift

Clinical and haematological aspects of cerebral venous thrombosis

1. Het blijft onduidelijk waarom een trombosebeen vaker voorkomt dan een cerebrale veneuze trombose (CVT). (dit proefschrift)

2. Voor het ontwikkelen van een prognostische score bij CVT-patiënten zou idealiter het natuurlijk beloop van een ziekte zonder behandeling moeten worden geobserveerd. Dit leidt echter tot ethische bezwaren. (dit proefschrift)

3. Het blijft lastig om de kleine groep van CVT-patiënten met een slechte uitkomst door middel van een prognostische score te voorspellen. (dit proefschrift)

4. Een goede uitkomst wordt in veel CVT-studies gedefinieerd als een score op de modified Rankin Scale van 2 of kleiner. Dit zegt echter alleen iets over de onafhankelijkheid van zorg in het dagelijks leven, maar geeft geen informatie over de minder zichtbare restklachten. (dit proefschrift)

5. Het gebruik van 'recalcified' bloed voor de trombo-elastograaf heeft 'praktische' voordelen, maar het effect hiervan op 'trombofiele' samples is onduidelijk. (dit proefschrift)

6. De *JAK2*-V617F mutatie is niet geassocieerd met CVT in afwezigheid van een myeloproliferatieve ziekte. (dit proefschrift)

7. Een verminderde veneuze afvloedcapaciteit is mogelijk een oorzaak voor de hoofdpijn na een CVT. (dit proefschrift)

8. Alle genetica is per definitie observationeel. In het genetisch onderzoek valt er niets te randomiseren. (Prof. dr. J.P. Vandenbroucke, NRC Handelsblad 6 juni 2009)

9. Cerebrale angiografie kan geen onderscheid maken tussen primaire angiitis van het centrale zenuwstelsel en het reversibele cerebrale vasoconstrictie syndroom.

10. Thunderclapheadache ('donderklapshoofdpijn') is een symptoom en geen diagnose.

11. With jaws on the end of a trunk, and five eyes, opabinia was like nothing that lives today. (Darwinjaar 2009)

12. Een flexibele instelling is een illusie.

13. De hoek van inval is niet altijd de hoek van uitval.

Karen Koopman, december 2009

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Things should be made as simple as possible. But not simpler.

Albert Einstein (1879-1955)

CONTENTS

1

GENERAL INTRODUCTION

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare disease. It can affect all ages and both sexes, but is most common in young women. The clinical presentation varies widely. Because of this, CVT can mimic many other conditions. Numerous factors have been associated with CVT. Neuroimaging has become essential in confirming CVT. Current treatment consists of anticoagulation (AC). The outcome is good in the majority of patients. Despite this good prognosis, CVT is still a challenging entity as its aetiology is only partially understood.

HISTORY

The first detailed description of a patient with CVT was probably in 1825. The French physician Ribes reported a 45-year-old man who died after a six months history of headache, seizures and delirium. Post mortem examination showed thrombosis of superior sagittal sinus, left lateral sinus and a cortical vein in the parietal region[1].

CVT was long thought to be lethal, since diagnosis was made by autopsy. The introduction of cerebral catheter angiography in the middle of the twentieth century showed that the incidence of CVT was higher and the outcome more benign than previously thought from autopsy series[2]. This was further supported by the development of non-invasive imaging of the venous system in the eighties and nineties of the last century.

EPIDEMIOLOGY

The current estimated annual incidence of CVT is 3 to 5 per million in adults and about 7 per million in children[3-5]. There are no reliable data concerning geographical or racial differences in the incidence[6]. CVT accounts for about 0.5-1% of all strokes and is an uncommon site of venous thromboembolism (VTE). In comparison, thrombosis in the deep veins of the lower legs (DVT), the most usual site, has an annual incidence of about 120 per 100,000 [7]. Arterial stroke and DVT are diseases of aging[6,7]. In contrast, CVT can occur at any age but is most common in women, particularly in the age group between 20 to 35 years. In children and the elderly there are no clear sex differences[6].

ANATOMY AND THROMBUS LOCATION

The cerebral venous system can be divided into a superficial and deep system. The superficial system comprises the dural sinuses and cortical veins and drains the cortical surfaces. The superior sagittal sinus lies in the median plane under the midline of the falx cerebri, runs posteriorly and inferiorly to the confluence of sinuses, where the superficial drainage joins with the deep venous system. From here, two transverse sinuses bifurcate and travel laterally and inferiorly in S-shaped

curves that form the sigmoid sinuses, which go on to form the two jugular veins. The cavernous sinuses communicate with the transverse and sigmoid sinuses. The deep system drains the deep white and grey matter and consists of deeper veins that join to form the great cerebral vein (vein of Galen). This vein merges with the inferior sagittal sinus to form the straight sinus which then joins the superficial system at the confluence of sinuses.
The veins of the brain have a thin wall without muscular tissue. In contrast to the veins of the lower legs, the cerebral veins have no valves.

The variability of the anatomy may complicate the diagnosis of CVT. Most importantly, the right lateral system is often larger than the left system and it can be difficult to distinguish pre-existent hypoplasia from CVT. Other examples of anatomic variations include the number and course of the superficial cortical veins and the course of the veins from the posterior fossa, which drains into the great cerebral vein and in the communicating veins of the cavernous sinus with the transverse sinus[3,8,9].

In most CVT patients, thrombosis occurs in more than one sinus. The superior sagittal sinus is involved in 72-92% of CVT. Thrombosis of the deep venous system is seen in about 10%. The lateral system is involved in about 80%. Isolated cortical vein thrombosis has been described in 2-5%. Cavernous sinus thrombosis is rare and represents less than 2% of CVT[3,10].

CLINICAL FEATURES

CVT can present with a wide spectrum of symptoms. Onset is usually subacute, but can be acute. In comparison with arterial stroke, CVT presents more progressive and symptoms tend to fluctuate.
The clinical features of CVT consist in essence of headache, focal deficits, seizures and impairment of consciousness, in various combinations and degrees of severity. The symptoms depend on the extension and localization of the thrombus and the collateral blood flow. The most frequent symptom of CVT is headache, which is present in 75-95% of all patients. Headache can be the only symptom or precedes the development of other signs. Headache onset is usually gradual, increasing over several days, but can also start suddenly, indistinguishable from headache in patients with subarachnoid haemorrhage[11,12]. Headache caused by intracranial hypertension from CVT is typically characterized by severe, dull, generalized pain. This can be accompanied by vomiting and visual disturbances due to papilloedema[12]. Elderly CVT patients present less often with headache, probably due to brain atrophy or diminished pain perception[13]. In about half of the patients focal neurological signs occur. These include motor, sensory deficits and aphasia. Focal neurological signs are mainly associated with venous infarction. In comparison with arterial stroke, venous infarction does not fit an arterial territory and often shows haemorrhagic transformation (seen in about 80% of the CVT patients with a venous infarction)[9,14]. Seizures are more frequently seen in CVT than in arterial stroke and occur in

about 40%. Seizures are usually generalized in patients with isolated intracranial hypertension and focal in patients with focal deficits. Disturbance of consciousness or cognitive dysfunction can be seen in CVT of the deep venous system. Patients may become comatose due to thalamic infarction or brain stem compression. Cranial nerve palsies are reported in 12% of the patients with CVT, but are rarely the only sign[10,15].

The following (overlapping) patterns have been described in decreasing frequency: isolated intracranial hypertension with headache and papilloedema; headache with focal neurological deficits/seizures; isolated cranial nerve lesions with headache; subacute unspecific encephalopathy; sinus cavernous syndrome with chemosis, protrusion bulbi and painful ophthalmoplegia[4,10,15].

AETIOLOGY AND PATHOPHYSIOLOGY

CVT is a multicausal disease. Many factors are associated with CVT that may contribute to formation of the thrombus (Table 1.1). The majority of the patients have at least one risk factor. Multiple risk factors are found in about half of the CVT patients and can have a synergistic effect[3,14]. In about 15% of the patients, no risk factor can be identified[16]. It is also unclear why a thrombus is more often located in the deep veins of the legs than in the brain. Other until now unknown factors may play a role. The risk factors are related to the Virchow triad of stasis of the blood, changes in the vessel wall and changes in the composition of the blood[17,18]. The risk factors are often classified into genetic factors and acquired factors. This classification is somewhat artificial, since some risk factors and associated diseases are influenced by genetic and acquired causes[19].

The pathophysiological process occurring after thrombus formation in CVT is not fully understood. The thrombosis of the veins themselves causes congestion of blood, which may lead to vasogenic oedema. Congestion can lead to venous infarction, which often transforms into haemorrhagic infarction and cytotoxic oedema. Furthermore, thrombosis of the sinuses leads to impaired absorption of cerebrospinal fluid in the arachnoid villi and increases intracranial pressure[3,9,17,20].

Genetic risk factors

Identified hereditary tendencies to thrombosis include antithrombin (AT) deficiency, protein C deficiency, protein S deficiency, factor V Leiden mutation (FV Leiden), prothrombin G20210A mutation (prothrombin G20210A) and elevated plasma levels of factor VIII (FVIII).

Heterozygosity of FV Leiden is found in about 5% of the general population. A meta-analysis reported an odds ratio (OR) for CVT in patients with FV Leiden of 3.38 (95% confidence interval (CI) 2.27-5.05)[21]. In comparison, heterozygosity of FV Leiden gives a 5-fold increased risk for VTE. Homozygosity of FV Leiden gives a 50-fold increased risk for VTE[22,23].

Prothrombin G20210A increases the risk forVTE. The estimated OR for VTE is 3.8 (95% CI 3.0-4.9)[24]. A

Table 1.1 Risk factors for cerebral venous thrombosis

Genetic risk factors
Antithrombin deficiency
Protein S deficiency
Protein C deficiency
Factor V Leiden mutation
Prothrombin G20210A mutation
Elevated plasma levels of factor VIII (> 1.50 U/ml)[a]
Acquired risk factors
Oral contraceptives
Hormonal replacement therapy
Pregnancy/puerperium
(Local) infection
Mechanical causes (head trauma/surgery/lumbar puncture)
Associated diseases
Solid malignancy
Myeloproliferative disorders
Leukaemia
Paroxysmal nocturnal haemoglobinuria
Sickle-cell trait
Antiphospholipid antibody syndrome
Systemic lupus erythematosis
Sarcoidosis
Inflammatory bowel disease (Morbus Crohn, colitis ulcerosa)
Behçet's syndrome
Wegener's granulomatosis
Thyroid diseases
Nephrotic syndrome

[a] Elevated plasma levels of factor VIII can also have an acquired cause

meta-analysis found an OR for CVT of 9.27 (95% CI 5.85-14.67)[17,21,25].

Deficiencies of protein C, protein S and AT are rare and it is estimated to increase the risk of DVT by about 10-fold[17]. A meta-analysis of a few studies with an overall low number of patients, reported combined OR for CVT of deficiencies of AT, protein C and protein S of 2.69 (95% CI 0.66-10.96), 11.10 (95% CI 1.87-66.05) and 12.49 (95% CI 1.45-107.29), respectively[21].

Elevated plasma levels of FVIII give a 3- to 4-fold increased risk for VTE for levels greater than 150% of normal (> 1.50 U/ml). A case-control study also reported higher levels of FVIII in CVT patients compared to controls[26]. Increased FVIII concentrations can be caused by acquired and inherited factors. The persistence of elevated FVIII levels over time suggests a genetic cause[17,27].

Acquired risk factors

Acquired risk factors for CVT include oral contraceptive (OC) use, hormone replacement therapy, pregnancy, puerperium, (local) infections, surgery, trauma and associated diseases, like malignancy, haematological disorders, antiphospholipid syndrome (APS) and other autoimmune diseases. Age and immobilization are important risk factors in DVT, but their role is less clear in CVT[18,19].

A meta-analysis found a strong association between OC use and CVT with an OR of 5.59 (95% CI 3.95-7.91)[21]. Third-generation progestins, desogestrel and gestodene, are thought to carry a higher risk for VTE and one study also found this for CVT[28-30]. The risk of CVT in women who use OC is larger if there is an additional hereditary prothrombotic factor[31,32].

Hormone replacement therapy has been associated with about a 2-fold risk for VTE, but little is known about the association with CVT[33,34].

CVT during pregnancy and puerperium occurs more often during the third trimester or puerperium[35]. The risk for VTE in pregnant women is 0.025 to 0.10%, which is 4 to 50 times higher than in non-pregnant women. The estimated risk for CVT in USA is 11.6 cases per 100,000 deliveries (0.012%)[36]. In the International Study of Cerebral Vein and Dural Sinus Thrombosis (ISCVT), a large multicentre study of 624 CVT patients, pregnancy or puerperium was seen in 77 of 381 women (20%) aged between 16 and 49 years[14]. Hormonal changes may play a role, as well as associated factors such as caesarean delivery, fluid disbalance, electrolyte- and acid-base disorders, hypertension and the presence of a hereditary prothrombotic factor[19,36,37].

Local and systemic infections can be complicated by CVT. With the introduction of antibiotics, the incidence has decreased, but it is still an important risk factor especially in children. Local infection was found in 28 of 160 children (18%) and in 21 of 42 children (50%) with CVT [5,38]. In the ISCVT, it was found in 64 of 624 patients (10%) older than 15 years[14].

Mechanical factors, including local head or neck trauma and surgery, especially penetrating head trauma and skull fractures, jugular catheter and lumbar puncture are risk factors for CVT. A mechanical cause was seen in 28 of 624 patients (4%) in the ISCVT[14,19].

Associated diseases

VTE occurs in 5% of the patients with cancer. The risk of thrombosis may be due to the production of substances with procoagulant activity, as well as the use of certain drugs, surgery and local factors. Sometimes, VTE can precede the diagnosis of malignancy. CVT has been associated with central nervous system (CNS) tumours, systemic malignancies and solid tumours outside the CNS. In the ISCVT, a malignancy was present in 46 of 624 patients (7%) with CVT (of whom 14 patients with a CNS tumour and 18 patients with a haematological malignancy)[14]. Paroxysmal nocturnal haemoglobinuria has also been associated with CVT[39,40].

Antiphospholipid antibody syndrome (APS) is an autoimmune disorder characterized by recurrent arterial and venous thrombosis, morbidity during pregnancy such as recurrent spontaneous abortion, in combination with the repeated presence of at least one type of autoantibody known as an antiphospholipid antibody (aPL). APS can occur as a primary condition or in association with an

underlying disease, particularly systemic lupus erythematosis[41]. The presence of aPL is a risk factor for CVT and it has been reported in 6 to 23% of the CVT patients[14,16,25,42].
CVT is associated with many other autoimmune disorders, including inflammatory bowel disease, Behçet's syndrome and vasculitis. CVT in patients with nephrotic syndrome and thyroid diseases has also been reported[19].

Indefinite factors
Hyperhomocysteinemia can have a genetic or acquired cause and has been associated with an increased risk for thrombosis[21,25]. A meta-analysis reported an OR for CVT of 4.07(95% CI 2.54-6.52)[21]. However, the association between hyperhomocysteinemia and VTE is controversial and may be explained by co-incidence with other thrombophilic factors, such as elevated plasma levels of FVIII. This is supported by the fact that studies failed to show a reduction in the risk of VTE by lowering plasma homocysteine[43,44].
Myeloproliferative disorders (MPD) are haematological malignancies that have been associated with an increased risk for thrombosis, including CVT. In some forms of MPD, the *Janus kinase 2* V617F (*JAK2*-V617F) mutation is found[45]. Thrombosis of the splanchnic veins has been associated with *JAK2*-V617F mutation in patients with and without overt MPD[45,46]. Several small studies investigated the role of *JAK2*-V617F in CVT patients, irrespective of MPD, with variable results. Thus far, no definite conclusions can be made about the association of *JAK2*-V617F mutation in itself and CVT[47-53].

DIAGNOSIS

Investigations should focus on establishing the diagnosis and searching for underlying causes and risk factors by a thorough (family) history and laboratory testing of known thrombophilic factors.

Imaging
The diagnosis of CVT is essentially based on neuroimaging. Magnetic resonance imaging (MRI) combined with venography (MRV) or computed tomography (CT) with venography (CTV) have largely replaced invasive cerebral angiography. Only if the diagnosis is still uncertain or in case of endovascular treatment, cerebral angiography is indicated[54].
CT of the brain performed on an emergency basis is usually the first investigation. CT of the brain can indicate both the venous thrombosis itself and the resulting oedema or (haemorrhagic) infarctions, but is normal in about 25-40% of the CVT patients. A dense triangle or cord sign in the confluence is seen in up to 60% and CT after contrast shows the empty delta sign in about 20-30% of the patients. A false-positive sign can be produced by fenestrations or septa within the dural sinus[9,55].
MRI findings depend on the sequence used and the stage of the thrombosis (Table 1.2; Figures 1.1 and 1.2). During the first 5 days, the thrombus is isointense on T_1-weighted and hypointense on T_2-weighted images. Between day 6 and 21, the thrombus becomes hyperintense, initially on T_1-

Table 1.2 MRI signal intensity of the thrombus

Stage	Acute (up to 5 days)	Subacute (day 6-21)	Chronic[a] (> 21 days)
Sequence			
T_1-weighted	Isointense	Hyperintense	Isointense
T_2-weighted	Hypointense	Hyperintense	Iso-, hyperintense

[a]Variable inhomogeneous signal, (partial) recanalization

weighted and subsequently on T_2-weighted images. After about a month, the thrombus signal is variable and may become isointense on T_1-weighted and isointense to hyperintense on T_2-weighted images. Also, (partial) recanalization can be seen[4,9]. Sensitivity may be increased by using gradient echo T_2*-weighted MRI sequences, on which the thrombus is hypointense during the acute and subacute stages[9,56,57]. MRI after contrast administration can show a delta sign, similar to the empty delta sign on post-contrast CT. MRI is more sensitive than CT in detection and characterization of parenchymal changes[9,55]. Venous oedema or infarction appear hyperintense on T_2-weighted images. Associated haemorrhage is hyperintense in the acute stage and hypointense in the subacute stage on T_2-weighted images. Diffusion-weighted imaging in combination with apparent diffusion coefficients can show, in contrast to arterial stroke, a combination of vasogenic and cytotoxic oedema[9,20].

MRV with time of flight or phase contrast techniques is mostly used for direct visualization of the venous system. Absence of flow signal and non-opacification is suggestive for thrombosis. The thrombus itself often appears hyperintense and may be difficult to distinguish from flowing blood with time of flight. Furthermore, the diagnostic value is limited because MRV can sometimes not differentiate between thrombosis and existing hypoplasia, especially in lateral sinuses. Correlation with T_1-weighted and T_2-weighted images can be helpful, as well as the use of gadolinium-enhanced MRV[58,59]. CTV may be a good alternative. It is less time-consuming but disadvantages are the use of intravenous contrast and ionizing radiation. It has been shown to be as accurate as MRV and may be superior in visualizing sinuses or smaller cerebral veins or cortical veins with low flow[9,58,60]. This technique is not used routinely at present.

Ultrasound

Transcranial Doppler sonography and transcranial colour-coded duplex sonography (TCCS) are non-invasive techniques that have potential utility for the diagnosis and follow-up of CVT. In the acute phase of CVT, ultrasonography can show a lack of signal or signs of venous collateral flow. The rate of abnormalities ranges from 50 to 100%. The use of contrast improves visualization[61-67]. However, ultrasonography cannot adequately differentiate between thrombosis and hypoplasia. Ultrasound can be useful in follow-up examinations; both an initially normal and normalization of TCCS have been associated with a good outcome[62,63].

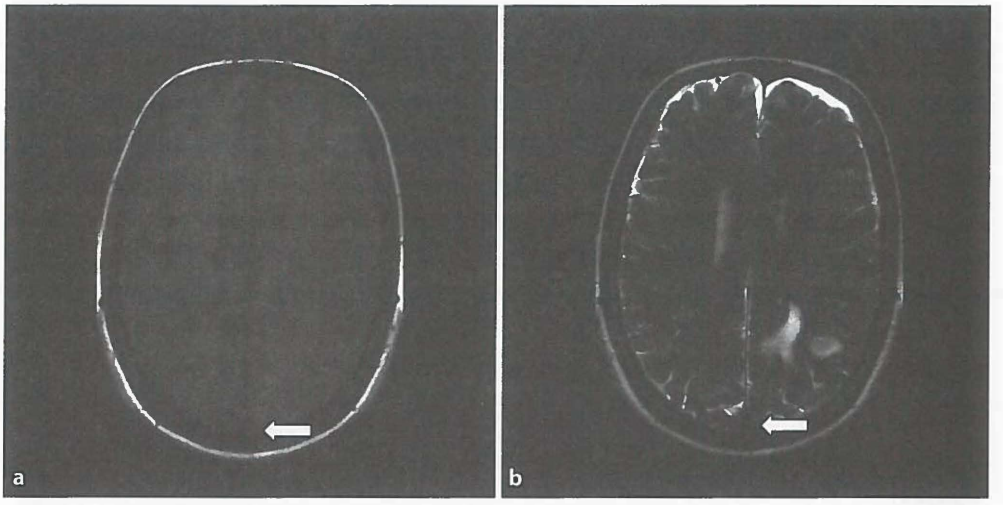

Figure 1.1 Acute thrombus (arrow) in sagittal superior sinus appears isointense on T1-weighted image (a) and hypointense on T2-weighted image (b)

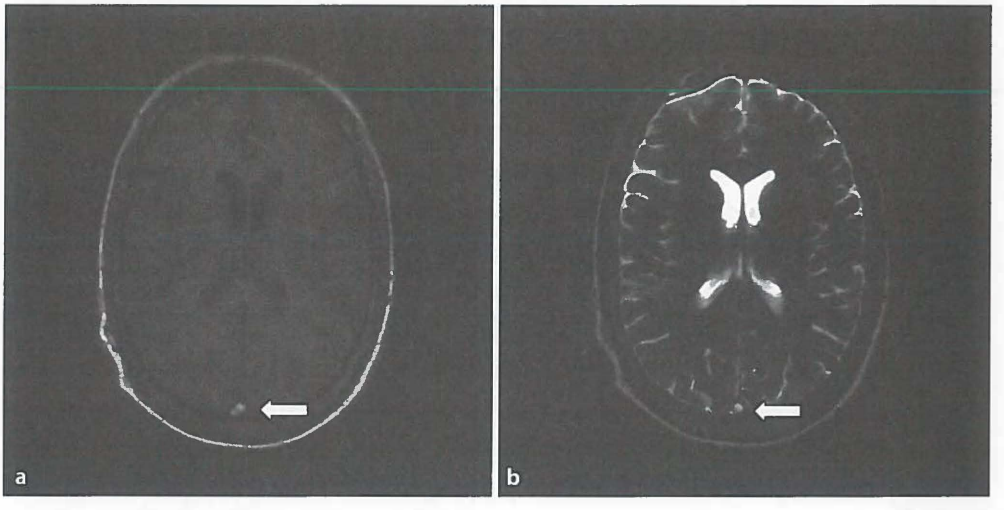

Figure 1.2 Subacute thrombus (arrow) in sagittal superior sinus appears hyperintense on T1-weighted image (a) and T2-weighted image (b)

Laboratory tests

Examination of the cerebrospinal fluid (CSF) is often aspecific. Abnormalities include raised CSF opening pressure in up to 85% and increased protein content, the presence of red blood cells and pleiocytosis in up to 50%. It does not necessarily help in establishing the diagnosis but can be important to rule out other conditions such as meningitis or subarachnoid haemorrhage[14,68].

D-dimer is a useful tool in the diagnosis of DVT of the legs and pulmonary embolism (PE), because low D-dimer levels have a high negative predicted value for DVT and PE[69,70]. However, this is less clear in CVT.. An elevated D-dimer level (>500 ng/ml) supports the diagnosis, but D-dimer levels are normal in about a quarter of CVT patients presenting with isolated headache[71,72].

Thromboelastography

It would be of interest to investigate whether CVT patients show an overall thrombotic tendency, compared to controls. A method of testing the coagulation of blood is thromboelastography (TEG). TEG is performed on whole blood and monitors the haemostatic process. It measures time to clot initiation and speed and strength of clot formation. TEG has been shown to provide additional information on thrombotic tendency in comparison with conventional laboratory tests[73-75]. The value of TEG has never been studied in CVT patients.

TREATMENT

Treatment options for CVT can be divided into treatment of the thrombosis, treatment of the underlying causes and symptomatic treatments of seizures or raised intracranial pressure[76].

Anticoagulants

The aims of AC treatment are to prevent the propagation of the thrombus and to prevent recurrence of CVT or thrombosis in other parts of the body. However, the use of AC may promote or worsen intracranial haemorrhages (ICH), which are common in CVT patients. Because CVT is a rare disease, no large randomized controlled trials are available. A meta-analysis of two small trials showed a not significant trend in reduction of poor outcome (pooled relative risk (RR) of death 0.33; 95% CI 0.08-1.21; pooled RR of death or dependency 0.46; 95% CI 0.16-1.31) and no promotion of ICH in patients treated with AC[77]. Current advice is that CVT patients with or without ICH should be treated either with body weight-adjusted subcutaneous low molecular weight heparin (90 anti-factor Xa U/kg bi-daily) or dose-adjusted intravenous heparin aimed at doubling activated partial thromboplastin time. After the acute phase, oral AC with a target INR of 2.0-3.0 is given, in the absence of contraindications. The optimal duration of AC is unknown. In line with VTE, AC may be given for 3 to 6 months if CVT was secondary to a transient risk factor and 6 to 12 months if CVT was idiopathic or in case of a mild hereditary thrombophilia. Long-term treatment should be considered in patients with recurrent VTE or severe hereditary thrombophilia such as deficiency of antithrombin, protein C or protein S or homozygosity of FV Leiden[6,76,78,79].

Acute recanalization therapy

Chemical thrombolysis

Thrombolytic therapy in CVT is thought to promote rapid recanalization. Systemic thrombolysis has proven its efficiency in the acute treatment of arterial stroke[80]. However, thrombolysis may carry a high risk of ICH, particularly in patients with a pre-treatment ICH[81]. There is insufficient evidence about the efficacy and safety of the standard use of systemic or local thrombolysis in CVT and there are no data from randomized controlled trials[82]. A review of case reports and uncontrolled trials, mostly using local thrombolysis, suggested a possible benefit of thrombolytic therapy in comatose patients[83]. If these patients deteriorate despite AC thrombolytic therapy may be considered[76].

Mechanical thrombectomy

Mechanical thrombectomy may have a lower risk of bleeding complications compared to thrombolysis. Balloon catheter thrombectomy has been used effectively, but a limitation is the risk of endothelium damage[84,85]. Rheolytic thrombectomy is based on the creation of a negative pressure with fragmentation and aspiration of the thrombus, and may be a better, less traumatic alternative[86]. Thrombectomy has also been described in combination with chemical thrombolysis. There are no randomized controlled trials on thrombectomy in CVT, but several case reports have shown good results in severely affected patients[86-88].

Symptomatic treatment

Seizures are common in CVT but there are no data regarding the effectiveness and duration of prophylactic antiepileptic drugs (AED). If seizures occur in the acute phase, AED should be started. Prolonged treatment for 1 year may be given in patients with early seizures and haemorrhagic lesions.

Lumbar puncture with CSF removal should be performed before starting AC in patients with isolated intracranial hypertension, if papilloedema threatens vision. If intracranial pressure is severely raised, general therapy of raised intracranial pressure is recommended, including head elevation at about 30 degrees, controlled hyperventilation and intravenous osmotic diuretics. There is no indication for the use of steroids[89]. Decompressive hemicraniectomy can be life saving in severely affected patients with impending herniation due to parenchymal lesions[76].

PROGNOSIS

In comparison to arterial stroke, the outcome of CVT is usually considered good with approximately 80% of the patients regaining functional independence[3,4,14,90]. Mortality is about 4% in the acute phase, mostly due to transtentorial herniation secondary to parenchymal lesions or diffuse brain oedema. If death occurs after the acute phase, it is often due to an underlying disorder, such as cancer[4,91]. The mortality rate may be lower in CVT associated with pregnancy or puerperium[92].

In the individual CVT patient, the outcome is largely unpredictable. It would be of interest to have an instrument that could predict outcome in an individual patient to assist the clinician, who may often be inexperienced in this rare disease, in treatment decision-making and inform patient and family on outcome. In the ISCVT, long-term predictors for poor outcome (modified Rankin scale score > 2) were male sex, age older than 37 years, mental status disorder, coma, CNS infection, any type of cancer, thrombosis in the deep venous system and ICH[14]. These factors can be useful in daily practice, but have not been externally validated.

Despite the overall good outcome, patients are at risk for complications after the acute phase.

The risk of recurrence of any thrombotic event is about 7%, most commonly within 1 year after CVT. The reported percentage of patients with remote seizures range from 5 to 32% and are more common in patients who had early seizures. The frequency of headache after CVT ranges between 14 and 53%. The headache can be chronic or intermittent. The pathophysiological mechanism is not fully understood. It may be due to reduced capacity of the venous system, but this needs further clarification. Other complications include neurological deficits and rarely induction of a dural arteriovenous fistula[14,93-97].

There is little known about the long-term sequelae and psychosocial impact in CVT patients. One study with a mean follow-up of 18.5 months found cognitive impairment in 16 out of 47 CVT patients (34%) and 19 patients (40%) had reduced or stopped their work[98]. In another study of 34 CVT patients with a median follow-up of 3.5 years, all patients returned to work, but neuropsychological assessment revealed 3 patients (9%) with non-fluent aphasia and 6 patients (18%) with working memory deficits[97].

CONCLUSIONS

Although the knowledge about CVT has been growing during the last decades, many questions remain unanswered. CVT is still considered as a rare disease, although the introduction of neuroimaging shows that the incidence is higher and outcome more benign than previously thought. Clinical presentation is highly variable and outcome largely unpredictable. Many factors have been associated with the disease, but the pathophysiological mechanism is only partly understood. Further investigation of clinical and haematological aspects is required.

AIMS AND OUTLINE OF THE THESIS

This thesis aims to investigate several clinical and haematological aspects of patients with cerebral venous thrombosis (CVT).

In chapter 2, a description of the University Medical Centre Groningen (UMCG)-CVT patient cohort is given and compared with other published CVT cohorts.

The outcome of CVT is variable from good recovery in most patients to death. Some treatment options of CVT are invasive and carry a high risk. Therefore, it would be helpful to predict outcome in an individual patient. The International Study of Cerebral Vein and Dural Sinus Thrombosis (ISCVT), a large multicentre study of 624 CVT patients, identifies predictors for poor outcome. In chapter 3, a predictive outcome score based on the ISCVT predictors was developed and validated in the UMCG-CVT cohort.

Although most patients regain functional independency after CVT, there is little known about the long-term sequelae. Chapter 4 describes a case-control study about the frequency and psychosocial impact of headache, depression, fatigue and cognition in CVT patients with a good outcome after CVT.

CVT is an uncommon manifestation of venous thromboembolism (VTE) and it is unclear why a thrombus is far more often located in the veins of the lower legs than in the brain. In chapter 5, risk factors for thrombosis between CVT patients and patients with deep vein thrombosis and/or pulmonary embolism (DVT/PE) aged between 15 and 50 years were compared to get more insight in the mechanism of thrombus location.

By virtue of their presenting thrombosis, CVT patients may be considered 'thrombophilic' compared to controls. Thromboelastography (TEG), a laboratory technique that measures in whole blood the complete haemostatic process without separation of blood cells or proteins, could be informative in this regard. Chapter 6 describes the results of a case-control study of TEG in patients with a history of CVT to investigate a predisposition for thrombosis.

Thrombosis at several locations is a major complication of myeloproliferative disorders (MPD). CVT is a rare manifestation of VTE and has also been associated with MPD. Some forms of MPD are associated with the *Janus kinase 2* V617F (*JAK2*-V617F) mutation. Splanchnic vein thrombosis is another unusual site of thrombosis. The *JAK2*-V617F mutation has been found in patients without overt MPD. In chapter 7, the association of the *JAK2*-V617F mutation in CVT patients irrespective of MPD was studied in a patient series with a review of the literature.

In summary, this thesis aims to answer the following questions:

1. Is it possible to develop a score which could help to predict outcome in CVT patients? (chapter 3)
2. Do CVT patients with a good outcome experience long-term sequelae with impact on daily life? (chapter 4)
3. Are there differences in risk factors between CVT and DVT/PE patients aged between 15 and 50 years which could give more insight in site-specific thrombosis? (chapter 5)
4. Could TEG demonstrate a persistent hypercoagulable state in patients with a history of CVT? (chapter 6)
5. Is the *JAK2*-V617F mutation associated with CVT, irrespective of the presence of a MPD? (chapter 7)

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2

CEREBRAL VENOUS THROMBOSIS PATIENT COHORT

INTRODUCTION

The University Medical Centre Groningen (UMCG) registry of cerebral venous thrombosis (CVT) patients is described in this chapter. The UMCG is a tertiary referral centre for the Northern part of the Netherlands with an adherence of approximately 1.3 million people. The registry included CVT patients aged 15 years and older who were admitted or analysed in the UMCG. It was started in 1994 first alone recording the results of thrombophilia tests in search of a cause of CVT. Since 2002, it is an ongoing registry of CVT patients recording baseline characteristics, risk factors, treatment modus and follow-up data. The missing data of the period 1994-2002 were collected in retrospect.

METHODS

Demographics of the patients, medical and familial history with special attention to venous thromboembolism (VTE), clinical presentation, brain imaging findings, treatment modus, results of thrombophilia tests, exposure to transient risk factors, comorbidity, clinical outcome and follow-up data about the recurrence of thrombosis and seizures were registered.

Diagnosis

The diagnosis of CVT had to be confirmed by magnetic resonance imaging (MRI) with venography, computed tomography (CT) with venography, digital subtraction angiography (DSA), surgery or autopsy, according to the current diagnostic criteria[1].

Thrombophilia tests

Laboratory thrombophilia tests included deficiencies of antithrombin, protein C, protein S (type I), factor V Leiden mutation (FV Leiden), the prothrombin G20210A mutation (prothrombin G20210A), lupus anticoagulant and plasma levels of factor VIII (FVIII:C) and were performed at least 3 months after CVT. The patients did not use vitamin K antagonists and women were not pregnant and did not use oral contraceptives at time of blood collection.
Levels of total and free protein S, protein C, antithrombin and FVIII were expressed as percentage of the levels measured in pooled normal plasma set at 100%. Total protein S and protein C antigen levels were measured by enzyme-linked immunosorbent assay (reagents obtained from DAKO, Glostrup, Denmark)[2]. Activity of protein C (Berichrom Protein C, Dade Behring) and antithrombin (Coatest, Chromogenix, Mölndal, Sweden) was measured by chromogenic substrate assays. Protein S deficiency was defined by level of total protein S below 65%. Protein C deficiency was defined by reduced levels of protein C antigen (< 64%) and/or protein C activity (< 63%). Antithrombin deficiency was defined by antithrombin activity levels below 74%. FVIII:C was measured by 1-stage clotting assay and was considered increased at levels above 1.50 U/ml. FV Leiden and prothrombin G20210A were demonstrated by polymerase chain reaction[3,4]. Lupus anticoagulant was defined

by abnormal values of dilute Russell viper venom time, activated partial thromboplastin time and tissue thromboplastin inhibition, that normalized by adding phospholipids to the plasma[5].

Transient risk factors and comorbidity

Transient risk factors of CVT included the use of oral contraceptives, hormonal replacement therapy, pregnancy/puerperium, (local) infection, surgery, immobilization for more than 7 days and trauma. Associated diseases included among others solid and haematological malignancies and autoimmune disorders. The risk factor had to be present within 3 months prior to the CVT.

Follow-up

Follow-up visits were regularly performed at least 6 weeks, 6 months and 12 months after CVT. Clinical outcome was assessed with the modified Rankin Scale (mRS) at last follow-up with a maximum of 24 months. The mRS is considered as a global disability scale with 6 different grades. A mRS score ≤ 2 means a functionally independent outcome and was defined as a good outcome. Grade 3-5 was defined as moderate or severe handicap. Grade 6 as outcome means death[6]. Follow-up information about the recurrence of VTE or seizures was also recorded.

RESULTS

Clinical characteristics

In the period between January 1994 and March 2009, 98 CVT patients (77 women (79%)) were included in the registry. Baseline characteristics, clinical presentation, brain imaging findings with location of the thrombus and treatment modus are summarized in Table 2.1. The median age at time of CVT was 34.5 years (range 16-81). Eighty-three patients (87%) presented with headache and 37 patients (39%) had seizures. Coma (Glasgow coma score ≤ 8) was seen in 11 patients (12%). Diagnosis was established by CT and/or MRI with venography in 95 patients (97%) and by DSA in 2 patients (2%). A parenchymal lesion on CT and/or MRI was seen in 55 patients (57%), of which a haemorrhagic lesion in 33 patients (60%). Thrombosis of the deep venous system was seen in 15 patients (16%). In the acute phase, 2 patients (2%) received local thrombolysis and 2 patients (2%) underwent a hemicraniotomy. Eighty patients (82%) were treated with anticoagulants.

Risk factors

The results of thrombophilia tests and acquired risk factors are summarized in Table 2.2. Heterozygosity of FV Leiden was found in 14 patients (16%). Elevation of FVIII:C was found in 38 patients (48%). Protein C, protein S and antithrombin deficiency were rare and seen in 3 (3%), 1 (1%) and 0 (0%) patients, respectively. The most common transient risk factor was a hormonal factor, seen in 56 women (74%). Local infection was present in 12 patients (12%). In 12 patients (13%), no risk factor was identified.

Table 2.1 Characteristics of 98 CVT patients

Characteristic (missing values)	n (%)[a]
Median age (years) (range)	34.5 (16-81)
Women	77 (79)
History venous thromboembolism	15 (15)
Symptoms/signs (3)	
Headache	83 (87)
Visual disturbance	28 (29)
Seizures	37 (39)
Mental status disorder	33 (35)
Motor/sensory symptoms	49 (52)
Nauseas/vomiting	38 (40)
Glasgow coma scale 0-8	11 (12)
9-12	4 (4)
13-15	80 (84)
Parenchymal lesion (1)	55 (57)
Haemorrhagic	33 (34)
Location thrombosis (3)	
Superior sagittal sinus	53 (56)
Lateral sinus	58 (61)
Deep venous system	15 (16)
Bilateral	11 (12)
Treatment (1)	
None	12 (12)
Anticoagulants	80 (82)
Local thrombolysis	2 (2)
Anti platelet drugs	5 (5)
Craniotomy	2 (2)

CVT = cerebral venous thrombosis
[a] Unless otherwise indicated

Clinical outcome

Eighty patients (82%) had a functionally independent outcome (mRS score ≤ 2) at last follow-up (median 24 months; range 2-24) (Table 2.3). Six patients died during follow-up, of which 3 in the acute phase due to CVT and 3 patients due to an underlying condition (brain tumour in 2 patients, acquired immunodeficiency syndrome in 1 patient). Of 2 patients who received local thrombolysis, 1 patient died and 1 patient recovered to a mRS score of 1. Two patients who underwent a hemicraniotomy had a mRS score of 2 and 4 respectively. Long-lasting seizures were seen in 15 patients (16%). Eight patients (9%) had recurrent VTE, of which 1 patient CVT (1%).

Table 2.2 Risk factors in 98 CVT patients

Risk factor (missing values)	n (%)
Thrombophilia testing	
Antithrombin deficiency (7)	0 (0)
Protein S deficiency (7)	1 (1)
Protein C deficiency (7)	3 (3)
Factor V Leiden mutation (8)	14 (16)
Heterozygous	14 (16)
Homozygous	0 (0)
Prothrombin G20210A mutation (8)	3 (3)
Heterozygous	3 (3)
Homozygous	0 (0)
Factor VIII > 1.50 U/ ml (19)	38 (48)
Lupus anticoagulant (18)	2 (3)
Transient risk factors (1)	
Hormonal factor	56 (74[a])
Oral contraceptives	43 (57[a])
Hormonal replacement therapy	1 (1[a])
Pregnancy/puerperium	2/10 (16[a])
Trauma/immobilization/surgery	8 (8)
ENT/CNS infection	12 (12)
Associated diseases	
Malignancy	14 (14)
Immune disease	11 (11)
No risk factor identified (8)	12 (13)

CVT = cerebral venous thrombosis; ENT = ear/nose/throat; CNS = central nervous system
[a] Percentage among women

REVIEW OF THE LITERATURE

Literature search with PubMed and Embase revealed 9 cohort studies of CVT with more than 50 patients[7-15]. Table 2.4 summarizes this literature search. The UMCG-CVT cohort is comparable with the cohorts found in the literature with regard to age, female predominance and outcome. In one study of 182 CVT patients from the United States the percentage of patients without sequelae was remarkably low (27%)[13]. A possible explanation could be that one-year follow-up was available for only 96 of 182 patients (53%).

The International Study on Cerebral Vein and Dural Sinus Thrombosis

The largest CVT cohort published so far is the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) and will be discussed in more detail[8]. The ISCVT is a prospective multicentre international study of 624 CVT patients (465 women (75%)). The median age at time of diagnosis was 37 years (range 18-86). At presentation, 553 patients (89%) had headache, 232 patients (37%) had any paresis and 245 patients (39%) had seizures. Eighty seven patients (14%) presented with

Table 2.3 Outcome at last follow-up of 98 CVT patients

Outcome (missing values[a])	n (%)[a]
Median follow-up (months) (range)	24 (2-24)
Modified Rankin Scale score	
0	34 (35)
1	27 (28)
2	19 (19)
3	8 (8)
4	3 (3)
5	1 (1)
6	6 (6)
Veneus thromboembolism (4)	8 (9)
CVT	1 (1)
Seizures (4)	15 (16)

CVT = cerebral venous thrombosis
[a] Unless otherwise indicated

stupor or coma. On brain imaging, a parenchymal lesion was seen in 392 patients (63%), of which a haemorrhagic lesion in 245 patients (39%). The superior sagittal sinus was involved in 313 patients (62%). Thrombosis of the deep venous system was seen in 68 patients (11%). The left lateral sinus was involved in 279 patients (45%) and of the right lateral sinus in 257 patients (41%). In 78 patients (13%) patients, no risk factor was identified and 272 patients (44%) had more than one risk factor. In the acute phase, 13 patients (2%) were treated with local thrombolysis and 9 patients (1%) had decompressive craniotomy or haematoma evacuation. At last follow-up (median 16 months), 540 patients (87%) had a functionally independent outcome (mRS score ≤ 2) and 52 patients (8%) died. These ISCVT characteristics do not markedly differ with the UMCG-CVT cohort (Table 2.1-2.3).

In conclusion, the characteristics of the UMCG-CVT cohort are comparable with other published CVT cohorts. This implies that the UMCG-CVT cohort consists of a representative group of CVT patients.

Table 2.4 Published CVT cohorts

Study	Design (n)	Inclusion period	n	Female n (%)[a]	Median/mean age (years)	Median/mean FU (months)	Good outcome (mRS ≤ 2) n (%)[a]	Death n (%)[a]
Preter et al 1996[7]	Retrospective Single centre	1975-1990	110	59 (58)	39	39	66 (78)[b]	8 (9)
Ferro et al 2001[11]	Retro/ prospective Multi centre (20)	1980-1998	142	101 (71)	35	at discharge	127 (89)	9 (6)
De Bruijn et al 2001[9]	Prospective Multinational (2) Multi centre (14)	1992-1996	59	50 (85)	33	3	49 (83)	6 (10)
Breteau et al 2003[10]	Prospective Multi centre (2)	1995-1998	55	42 (76)	39	36	45 (82)	7 (13)
Ferro et al 2004[8]	Prospective Multinational (21) Multi centre (89)	1998-2001	624	465 (75)	37	16	540 (87)	52 (8)
Stolz et al 2005[12]	Retro/ prospective Single centre	1985-2001	79	61 (77)	39	6	56 (76)	12 (15)
Wasay et al 2008[13]	Retro/ prospective Multi centre (10)	1991-2001	182	109 (60)	38	12	26 (27)	24 (13)
Azin et al 2008[14]	Prospective Single centre	2000-2003	61	45 (74)	36	n.a.	n.a.	9 (15)
Khealani et al 2008[15]	Retro/ prospective Multinational (2) Multi centre (4)	1991-2007	109	58 (53)	35	6	61 (77)	11 (14)

CVT = cerebral venous thrombosis; FU = follow-up; mRS = modified Rankin scale; n.a. = not available
[a] Percentages are based on available values
[b] Outcome was not assessed with the mRS, number indicates patients with no neurological sequelae

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3

DEVELOPMENT AND VALIDATION OF A PREDICTIVE OUTCOME SCORE OF CEREBRAL VENOUS THROMBOSIS

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ABSTRACT

Background and Purpose

Cerebral venous thrombosis (CVT) is a rare disease with a variable outcome. The aim of this study was to develop and validate a predictive outcome score for CVT patients.

Methods

The score was based on the 8 predictive variables of poor outcome (modified Rankin Scale score > 2) from the International Study on Cerebral Vein and Dural Sinus Thrombosis: age > 37 years, male, mental status disorder, coma, intracranial haemorrhage, deep CVT, central nervous system infection and malignancy. To assign a weighted index (WI), the natural logarithm of the hazard ratio of each variable was calculated, multiplied by 10 and rounded to the nearest integer. The individual score of each patient was the sum of the WI. The validation sample consisted of a single centre cohort of 90 CVT patients.

Results

Sixteen patients (18%) had a poor outcome. The predictive outcome score had an area under the receiver operating characteristic curve of 0.81 (95% confidence interval (CI) 0.71-0.90). The cut-off score with the maximum sum of sensitivity and specificity was a score ≥ 14 with sensitivity of 88% (95% CI 81%-95%) and specificity of 70% (95% CI 61%-79%). The predictive value of a score < 14 for good outcome was 96% (95% CI 92%-100%), whereas the predictive value of a score ≥ 14 for poor outcome was 39% (95% CI 29%-49%).

Conclusions

This simple predictive outcome score may be useful in CVT patients. A cut-off score of 14 reliably predicts good outcome, but is less accurate in predicting poor outcome.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare disease with an estimated annual incidence of 3 to 5 per million which mainly affects young women[1,2]. The prognosis is highly variable from functional independency in about 80% of the CVT patients to severe disability or death[1,2]. Treatment options vary from no treatment to anticoagulants, catheter directed thrombolysis and symptomatic therapy of seizures and elevated intracranial pressure, including craniotomy[3]. Because of the rarity of CVT and the wide choice of treatment options of which some carry out high risk, it would be of interest to predict outcome in an individual CVT patient to assist the clinician in decision-making and to inform patients and family.

The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) identified 8 independent predictors of death or dependency[4]. The aim of this study was to develop a predictive outcome score based on the ISCVT predictors and to validate this score in a single centre cohort of CVT patients.

METHODS

Patients

The study cohort consisted of 90 consecutive CVT patients aged 15 years and older, who were evaluated in the University Medical Centre of Groningen between January 1994 and February 2007. CVT was diagnosed according to the current diagnostic criteria and had to be confirmed by magnetic resonance imaging (MRI) with venography (MRV), computed tomography (CT) with venography (CTV), digital subtraction angiography (DSA), surgery or autopsy[5]. The following information was registered: demographic data, medical history, clinical symptoms and signs, time to diagnosis, imaging modality, location of the thrombus, (haemorrhagic) parenchymal lesions, genetic and acquired risk factors, treatment and clinical course. Laboratory thrombophilia tests included deficiencies of antithrombin, protein C, protein S, factor V Leiden mutation, the prothrombin G20210A mutation, lupus anticoagulant and increased plasma levels of factor VIII (> 1.50 U/ml) and were performed > 3 months after CVT, end of use oral contraceptives and > 2 weeks after stopping vitamin K antagonists. Acquired risk factors included transient risk factors with CVT occurring within 3 months after exposure (oral contraceptive use, hormone replacement therapy, pregnancy/puerperium, infection (central nervous system, ear/nose/throat, other), surgery, immobilization, head trauma and associated diseases (malignancy or other systemic disorder).

Follow-up visits were regularly performed at least 6 weeks, 6 months and 12 months after the CVT. Poor outcome was defined as a score > 2 on the modified Rankin Scale (mRS) or death at last follow-up with a maximum of 24 months.

Predictive score

The score was based on the 8 independent predictive variables of poor outcome (mRS score > 2 or death) at last follow-up in the ISCVT[4]. To assign a weighted index (WI) for each variable, the natural logarithm of the hazard ratio (HR) of each variable was multiplied by 10 and rounded to the nearest integer to obtain easily applicable scores per variable (Table 3.1). The individual score of each patient was calculated by adding the WI of each variable present[6].

Table 3.1 ISCVT hazard ratio and weighted index for each predictive variable of poor outcome

Variable	Hazard ratio	Weighted index
Male sex	1.59	5
Intracranial haemorrhage	1.88	6
Mental status disorder	1.95	7
Age > 37 years	2.00	7
Glasgow coma score < 9	2.65	10
Malignancy	2.90	11
Deep cerebral venous thrombosis	2.92	11
Central nervous system infection	3.34	12

ISCVT = International Study on Cerebral Vein and Dural Sinus Thrombosis [4]

Statistical analysis

Since the methods for diagnosis and treatment might have changed during the last decades, the association between year of diagnosis and outcome of CVT was analysed with Spearman's correlation coefficient (ρ).

The sensitivity and specificity of all possible cut-off scores of the predictive score for outcome were investigated. Sensitivity was defined as the proportion of patients with poor outcome that were correctly identified by the score as likely to have poor outcome. Specificity was defined as the proportion of patients with good outcome that were correctly identified by the score. The predictive value for poor outcome was defined as the proportion of patients with a prognostic poor outcome score that were correctly predicted. The predictive value for good outcome was defined as the proportion of patients with a prognostic good outcome score that were correctly predicted. Discrimination of the predictive score was assessed with the area under a receiver operating characteristics curve. An area under the curve (AUC) above 0.8 was considered to reflect adequate discrimination between the 2 outcomes[7]. False poor and false good outcome rates were considered to be equally important and the score with the maximum sum of sensitivity and specificity was chosen as the cut-off score[8].

RESULTS

The main characteristics and outcome of the 90 patients are given in Table 3.2. The mean age was 36.2 years (range 16-81). The mean follow-up was 19 months. Sixteen patients (18%) had a poor outcome, of which 3 died in the acute phase and 3 died of an underlying condition (brain tumour in

Table 3.2 Baseline characteristics and outcome of 90 CVT patients

Characteristic	n (%)[a]
Mean age (years) (range)	36.2 (16-81)
Female	70 (78)
Median time until diagnosis (days)	8
Symptoms/ signs	
Headache	78 (87)
Visual disturbance	26 (29)
Seizures	36 (40)
Mental status disorder	30 (33)
Motor/sensory symptoms	47 (52)
Nausea/vomiting	37 (41)
Glasgow coma scale 9-15	79 (88)
< 9	11 (12)
Parenchymal lesion	53 (59)
Haemorrhagic	31 (34)
Location thrombosis	
Superior sagittal sinus	49 (54)
Lateral sinus	54 (60)
Deep venous system	14 (16)
Bilateral	10 (11)
Treatment	
None	12 (13)
Anticoagulants	73 (81)
Local thrombolysis	2 (2)
Anti platelet drugs	5 (6)
Craniotomy	3 (3)
Risk factors[b]	
Genetic without acquired factor	2 (2)
Acquired without genetic factor	53 (65)
Genetic and acquired factor	19 (23)
No risk factor identified	8 (10)
Outcome	
Mean follow-up (months) (median)	19 (24)
Modified Rankin Scale score 0-2	74 (82)
3-5	10 (11)
6	6 (7)
Recurrent venous thromboembolism	6 (7)
CVT	1 (1)

CVT = cerebral venous thrombosis
[a] Unless otherwise indicated
[b] 8 missing and 11 incomplete genetic screening

2 patients, acquired immunodeficiency syndrome in 1 patient). Diagnosis was established by MRI/MRV in 78 patients (89%), by CT/CTV in 8 patients (9%) and by DSA in 2 patients (2%). There was no correlation between time of diagnosis and outcome ($\rho = 0.036$; $p = 0.75$).

The HR of the predictive variables, as reported from the ISCVT, and the calculated WI are given in Table 3.1[4]. The individual scores of the patients ranged from 0-39 (median 12.5, interquartile range 6.75-18.0

The AUC of the predictive score was 0.81 (95% CI 0.71-0.90). The cut-off score with the maximum sum of sensitivity and specificity was a score ≥ 14 with sensitivity of 88% (95% confidence interval (CI) 81%-95%) and specificity of 70% (95% CI 61%-79%). The predictive value of a score < 14 for good outcome was 96% (95% CI 92%-100%). The predictive value of a score ≥ 14 for poor outcome was 39% (95% CI 29%-49%). From all the possible cut-off scores, Table 3.3 shows some arbitrary chosen cut-off scores stratified over the range to illustrate the effect on sensitivity, specificity and predictive value by choosing another (higher or lower) cut-off score than the optimal cut-off score.

Table 3.3 Sensitivity, specificity and predictive value of various cut-off scores

Score	n	mRS > 2	Sens	Spec	Sum	PV mRS > 2	PV mRS ≤ 2
≥ 7	68	16	1.00	0.30	1.30	0.24	1.00
≥ 14	*36*	*14*	*0.88*	*0.70*	*1.58*	*0.39*	*0.96*
≥ 21	19	8	0.50	0.85	1.35	0.42	0.89
≥ 28	9	4	0.25	0.93	1.18	0.44	0.85
≥ 35	4	2	0.13	0.97	1.10	0.50	0.84

mRS = modified Rankin Scale; Sens = sensitivity; Spec = specificity; Sum = sensitivity + specificity; PV = predictive value
In italics: cut-off score with maximum sum of sensitivity and specificity

DISCUSSION

This study demonstrates that this score may be useful in predicting the outcome of CVT patients. A cut-off score below 14 reliably predicts good outcome, but a score of 14 or above is less accurate in predicting poor outcome of CVT.. It is relatively simple in use, in the sense that it contains 8 variables that can be easily determined in a clinical setting. The score was based on the predictors of poor outcome at last follow-up of the ISCVT. The ISCVT is the largest prospective observational study in 624 CVT patients on outcome [4]. Because of the rarity of CVT, prospective validation with a suitable number of patients will take a long time. In this study a partly retrospective cohort of CVT patients for validating the outcome score was used. Despite this, the patient characteristics of the validation cohort did not seem to differ from the ISCVT cohort and other CVT cohorts with regard to age, sex

distribution and outcome and therefore validation may be acceptable[4,9-13].
A cut-off score of 14 implies that a patient at risk of poor outcome would have at least two of the predictors. This cut-off score was correct in predicting good outcome in 96%, but only 39% of the patients with a score above the cut-off score had a poor outcome. Taking into account the high a priori chance of good outcome, this cut-off score may be less accurate to select patients with expected poor outcome. The cut-off score was based on the assumption of equally importance of false good outcome and false poor outcome. By choosing a higher cut-off score one could slightly increase the predictive value for poor outcome, but the predictive value for good outcome would decrease.
The study has limitations. Firstly, the sample size of the studied cohort is relatively small and the results have to be interpreted with caution. Secondly, the predictors were identified as well as tested in a group of CVT patients who received variable treatments. Ideally, for the purpose of developing a predictive score of outcome able to select patients for adequate treatment, the natural course without any form of treatment should be studied. This study design does not appear feasible.

In conclusion, this simple predictive score for patients with CVT may be useful in predicting of outcome. Most importantly, a score below 14 accurately rules out poor outcome, but a score of 14 or above is less accurate in predicting poor outcome of CVT.

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4

LONG-TERM SEQUELAE AFTER CEREBRAL VENOUS THROMBOSIS IN FUNCTIONALLY INDEPENDENT PATIENTS

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ABSTRACT

Background and Purpose

The majority of survivors of cerebral venous thrombosis (CVT) regain functional independence, but it is unclear whether these patients experience long-term sequelae. The aim of this case-control study was to assess (1) the frequency of headache, fatigue, depression and concentration impairment, and (2) the impact of these sequelae on daily life and employment in functionally independent CVT patients.

Methods

Forty-four CVT patients aged 15 years and older, diagnosed between January 1997 and July 2006, who were functionally independent (modified Rankin scale score ≤ 2) at least 12 months after CVT, were included. Healthy controls were matched for age and sex. Headache was assessed by the Headache Impact Test, fatigue with the Fatigue Severity Scale, depression by the Centre for Epidemiological Studies Depression Scale and concentration impairment with the cognition dimension of the 6-dimensional EuroQol. The psychosocial impact (based on the Severity Impact Profile 68) and the impact on employment status were studied.

Results

Median follow-up was 63 months (range 12-124). Thirty-three patients (75%) reported concentration impairment, 19 patients (43%) had headache, 13 patients (30%) were depressive and 13 patients (30%) complained of fatigue. All sequelae were more reported by patients than controls. The sequelae were correlated with each other and with a higher psychosocial impact. Working was impossible for 8 (21%) and difficult for 13 (34%) of previously employed patients.

Conclusions

In this case-control study, CVT patients classified as having a good (independent) outcome often experience long-term complaints that have a negative impact on their psychosocial and employment status.

INTRODUCTION

Cerebral venous thrombosis (CVT) accounts for 0.5-1.0% of all strokes and mainly affects young women. In comparison to arterial stroke the outcome is usually considered good in the sense that about 80% of patients with CVT regain functional independence[1-3]. It is unclear, however, whether these patients experience long-term sequelae.

The aim of this case-control study was to assess (1) the frequency of headache, fatigue, depression and concentration problems, and (2) the impact of these sequelae on daily social life and employment status in patients with a functionally independent outcome after CVT.

METHODS

Patients

Data were derived from a single centre database of 74 consecutive CVT patients aged 15 years and older who were admitted to the University Medical Centre Groningen between January 1997 and July 2006. The follow-up schedule consisted of clinic visits at least 6 weeks, 6 months and 12 months after CVT. A functionally independent outcome was defined as a score ≤ 2 on the modified Rankin Scale (mRS). Patients with a mRS score ≤ 2 at least 12 months after the CVT were included. CVT had to be confirmed by magnetic resonance imaging with venography, computed tomography with venography, digital subtraction angiography or surgery, according to the current diagnostic criteria[4]. The following information was recorded in the database: demographics, medical history, clinical symptoms and signs, time until diagnosis, imaging modality, location of the thrombus, (haemorrhagic) parenchymal lesions, laboratory thrombophilia testing, acquired risk factors, comorbidity, treatment and clinical course.

Patients who met the inclusion criteria received a mail questionnaire. To ensure optimal matching, each CVT patient was compared with an age (+/- 3 years) and sex matched healthy control without a history of chronic diseases or psychiatric disorder.

Instruments

Sequelae

Headache was measured with the 6-item Headache Impact Test (HIT). A score > 56 has been shown to be clinically important (range 36-78)[5-7]. Fatigue was measured with the 9-item Fatigue Severity Scale (FSS). A FSS score ≥ 5 was defined as "fatigue" (range 0-7)[8,9]. The 20-item Centre for Epidemiological Studies Depression Scale (CES-D) was used to screen for depression. A score ≥ 16 was considered to denote depression (range 0-60)[10,11]. Concentration impairment was evaluated by using the "cognition" dimension of the 6-dimensional EuroQol (cognition EQ-6D)[12,13]. This dimension has 3 possible answers: no problems/some problems/extreme problems in concentration.

Psychosocial consequences and impact on employment

The psychosocial impact of the long-term sequelae was measured by the total scores on the psychological dimension (17 items) and social dimension (21 items) of the Severity Impact Profile 68 (SIP 68)[14,15]. The score was given as a percentage of checked items out of the total items, where a higher percentage indicated more impact.

Employment status was assessed by self-developed questions about the content of the work, as well as by working hours before and after the CVT. These questions were not included in the questionnaire for the controls.

Statistical analysis

The frequency of clinically important headache, fatigue, depression and concentration impairment in patients and controls were compared using the McNemar test. In addition, the exact scores on the HIT, FSS, CES-D and EQ-6D were compared using the Wilcoxon test.

Spearman correlation coefficients (ρ) were calculated to analyse the correlation between (1) the scores on the HIT, CES-D, FSS, cognition EQ-6D, (2) the mRS score of the patients and the various sequelae and (3) the psychosocial impact of the sequelae. A $\rho < 0.33$ indicate a weak correlation; $0.33 \leq \rho < 0.66$ indicate a moderate correlation and $\rho \geq 0.66$ indicate a strong correlation.

In the patients, responders and non responders were compared for age using the Mann-Whitney U test, for sex using the Fisher's exact test and for mRS score using the Kruskall-Wallis test.

In the responders (the included patient group), univariate analyses with the Chi-square test or Fisher's exact test on variables that may be associated with clinically important headache, fatigue, depression and concentration impairment were performed. These variables were male sex, age > 31 years, location of CVT (superior sagittal sinus, lateral sinus and deep venous system), any parenchymal lesion, intracranial haemorrhage, follow-up < 24 months, post CVT epilepsy, malignancy and systemic disorder. If significant associations were detected, the intention was to perform a multivariable analysis using a logistic regression model.

A 2-sided p-value < 0.05 was considered as statistically significant. All statistical analyses were performed with SPSS version 14.0 for Windows.

RESULTS

Fifty-six of 74 patients with CVT were functionally independent at least 12 months after CVT. Forty-four of these 56 patients returned the questionnaire (response rate 79%) and were included in the study with 44 age and sex matched controls. In the group of 12 patients (10 women) who did not return the questionnaire, the median age was 40.0 years (range 20-81). Five patients (42%) had a mRS score of 0, 3 patients (25%) had a mRS score of 1 and 4 patients (33%) had a mRS score of 2. There were no significant differences in age, sex distribution and mRS score between the responders and non-responders. Baseline characteristics of the included patients are given in Table 4.1.

Table 4.1 Characteristics of 44 CVT patients

Characteristic (missing value)[a]		n (%)[a]
Median age diagnosis (years) (range)		31.0 (16-68)
Women		36 (82)
Median time until diagnosis (days)		9.5
Symptoms/signs at admission (2)		
Headache		36 (86)
Visual disturbance		11 (26)
Seizures		13 (31)
Mental status disorder		18 (43)
Motor/sensory deficits		22 (52)
Nausea/vomiting		15 (36)
Glasgow coma scale	13-15	39 (93)
	9-12	1 (2)
	< 9	2 (5)
Parenchymal lesion (2)		29 (69)
Haemorrhagic		16 (38)
Risk factors (3)		
Genetic risk factor without acquired risk factor		1 (2)
Acquired risk factor without genetic risk factor		25 (61)
Genetic and acquired risk factor		7 (17)
No risk factor identified		6 (15)
Local risk factor		7 (17)
Follow-up		
Median time diagnosis-inclusion (months) (range)		63.0 (12-124)
mRS score 0		14 (32)
mRS score 1		17 (39)
mRS score 2		13 (30)
Seizures (2)		7 (17)
Venous thromboembolism (2)		3 (7)
CVT		1 (2)

CVT = cerebral venous thrombosis; mRS = modified Rankin Scale
[a] Unless otherwise indicated

Sequelae

The frequency of the sequelae and the mean scores of the HIT, CES-D, FSS and cognition EQ-6D are presented in Table 4.2. All sequelae were more frequently reported in the patient group than in the control group. Concentration impairment was the most common sequelae and reported by 33 CVT patients (75%) (3 with extreme impairment) and by 10 controls (23%) (none with extreme impairment).

Most sequelae were significantly associated with each other in both patients and controls. The correlation coefficients in the control group were lower compared to the CVT group (Table 4.3). In the patient group, mRS score was strongly associated with all sequelae scores. The univariate analyses revealed no variables that were significantly associated with headache, fatigue, depression or concentration problems in CVT patients (data not shown).

Table 4.2 Comparison of the sequelae between 44 CVT patients and 44 healthy controls

A	Patients n(%)	Controls n (%)	McNemar test p
Headache	19 (43)	4 (9)	0.001*
Fatigue	13 (30)	3 (7)	0.013*
Depression	13 (30)[a]	3 (7)	0.013*
Concentration impairment	33 (75)	10 (23)	<0.001*
B	**Mean (SD)**	**Mean (SD)**	**Wilcoxon test p**
HIT	51.0 (10.29)	43.3 (7.47)	<0.001*
FSS	4.16 (1.57)	2.79 (1.25)	<0.001*
CES-D	11.4 (8.44)[a]	6.25 (7.17)	0.001*
Cognition EQ-6D	1.82 (0.54)	1.23 (0.42)	<0.001*
SIP psychosocial *(% max score)*	7.43 (7.11) *(20)*	1.84 (2.98) *(4.8)*	<0.001*
SIP psychological	4.02 (3.98) *(24)*	0.82 (1.66) *(4.8)*	<0.001*
SIP social	3.41 (3.61) *(16)*	1.02 (2.27) *(4.8)*	<0.001*

CVT = cerebral venous thrombosis; HIT = Headache Impact Test; FSS = Fatigue Severity Scale; CES-D = Centre for Epidemiological Studies Depression Scale; Cognition EQ-6D = cognition dimension of the 6-dimensional EuroQol; SIP 68 psychosocial = psychological and social dimension of the Severity Impact Profile 68; % max score = % of the maximum score for the SIP

[a] 1 missing value

* $p < 0.05$

Psychosocial consequences and impact on employment

The mean scores of the psychological and social dimension of the SIP 68 were 24% and 16% of the maximum scores in CVT patients. The SIP scores were lower in the control group (Table 4.2). In the patient group, a higher psychosocial impact score on the SIP 68 was associated with a higher mRS score. Most sequelae scores were associated with a higher psychosocial impact (Table 4.3).

Of the employed patients before the CVT (n = 38), 8 patients (21%) did not return to work and 13 patients (34%) who returned to work reported more difficulties in their work.

Table 4.3 Spearman's correlation coefficients between scores on the HIT, CES-D, FSS, cognition EQ-6D, mRS and psychosocial SIP 68 in CVT patients and controls

CVT patients	HIT ρ (p)	FSS ρ (p)	CES-D[a] ρ (p)	Cognition EQ-6D ρ (p)	Psychosocial SIP 68 ρ (p)
FSS	*0.47* (0.001)*				
CES-D[a]	*0.39* (0.01)*	*0.43* (0.004)*			
Cognition EQ-6D	*0.47* (0.001)*	*0.59* (<0.001)*	0.28 (0.073)		
SIP 68 psychosocial	*0.51* (<0.001)*	**0.69** (<0.001)*	*0.52* (<0.001)*	**0.71** (<0.001)*	
mRS score	*0.55* (<0.001)*	**0.75** (<0.001)*	*0.48* (0.001)*	*0.65* (<0.001)*	**0.80** (<0.001)*
Controls					
FSS	0.28 (0.06)				
CES-D	*0.43* (0.004)*	*0.35* (0.02)*			
Cognition EQ-6D	0.22 (0.15)	*0.33* (0.031)*	0.31 (0.04)*		
SIP 68 psychosocial	*0.45* (0.002)*	0.27 (0.08)	*0.43* (0.004)*	*0.40* (0.008)*	

CVT = cerebral venous thrombosis; ρ = Spearman's correlation coefficient; HIT = Headache Impact Test; FSS = Fatigue Severity Scale; CES-D = Centre for Epidemiological Studies Depression Scale; cognition EQ-6D = cognition dimension of the 6-dimensional EuroQol; psychosocial SIP 68 = psychological and social dimension of the Severity Impact Profile 68; mRS = modified Rankin Scale
In bold: strong correlation (ρ ≥ 0.66)
In italics: moderate correlation (0.33 ≤ ρ < 0.66);
[a] 1 missing value
* p < 0.05

DISCUSSION

This case-control study demonstrates that functionally independent CVT patients often experience long-term sequelae. About 75% of the CVT patients reported concentration problems and about half of them reported headache. Fatigue and depressive symptoms were present in 30% of the patients. These symptoms were all less frequently reported in the control group. All sequelae had an impact on the patient's psychosocial functioning and employment status.

Only a few studies reported long-term effects in CVT patients, but none of these focused on functionally independent patients and compared the sequelae with healthy controls. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), severe headache occurred in 38 patients (14%) with median follow-up 16 months[16]. Other studies reported frequencies between 14 and 53%[16-19]. In this study on independent patients, clinically important headache was found in

46% of the patients. In a long-term outcome study of 47 CVT patients with a mean follow-up of 18.5 months, 16 patients (34%) had significant cognitive impairment, assessed with the Minimal Mental State Examination and specific cognitive tests and 19 (40%) had reduced or stopped their work [20]. This study confirms the presence of work-related problems after CVT. Another study of 34 CVT patients with a median follow-up of 3.5 years, neuropsychological assessment revealed 3 patients (9%) with non-fluent aphasia, 6 patients (18%) with working memory deficits and 6 patients (18%) with depression, assessed by the Beck Depression Inventory. All patients could resume their work[19]. There are no other studies about the occurrence of depression or fatigue in patients after CVT. This study suggests that one out of three functionally independent CVT patients experiences fatigue or depression.

Most of the previous studies defined outcome in CVT using global disability scales, like the mRS, which is commonly used as endpoint in stroke studies. An mRS score ≤ 2, which reflects a functionally independent state, is often considered as a good outcome[21]. Although the sequelae were more reported in the patients with a higher mRS score, the use of the mRS to assess outcome in CVT may not sufficiently make aware of the importance of these common, but less obvious, sequelae of CVT.

The study has limitations. Firstly, there may be a patient bias because about 20% of the announced patients did not return the questionnaire. There were, however, no differences in age, sex distribution and mRS score between responders and non-responders. Secondly, the findings are based on mail questionnaire and self-reported experiences and concentration problems could have been measured more objectively and in more detail by neuropsychological testing. Nevertheless, the reported problems are the perception of the patient and may be relevant, because it represents the problems encountered in daily life. Thirdly, the limited sample size restricts the analysis of possible explanatory factors for headache, fatigue, depression and concentration problems.

This case-control study showed that, in the long-term follow-up of patients with an apparently good outcome following CVT, attention should be paid to concentration difficulties, headache, fatigue and depression. Further investigation is required to study pathophysiological mechanisms and optimal management of these symptoms.

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5

Risk factors for cerebral venous thrombosis and deep venous thrombosis in patients aged between 15 and 50 years

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ABSTRACT

Background and purpose

Cerebral venous thrombosis (CVT) and deep venous thrombosis and/or pulmonary embolism (DVT/PE) are associated with many risk factors. It is unclear why CVT occurs less often than DVT/PE. Age-dependent risk factors may play a role. The aim of this study was to compare risk factors in a uniform age group of CVT and DVT/PE patients aged between 15 and 50 years.

Methods

Thrombophilic markers and clinical risk factors of 79 CVT patients and 173 DVT/PE patients aged between 15 and 50 years were compared. Multivariable logistic regression analysis was performed to investigate if risk factors were independently associated with CVT or DVT/PE.

Results

CVT patients were younger (median age 30 years versus 42 years; $p < 0.001$) and more often female (82% versus 52%; $p < 0.001$). There were no significant differences in thrombophilic markers. CVT was less often associated with trauma, immobilization or surgery than DVT/PE (6% versus 21%; adjusted odds ratio (OR) 0.29; 95% confidence interval (CI) 0.10-0.82). In women, CVT was more frequently associated with OCuse, pregnancy or puerperium (82% versus 53%; adjusted OR 2.34; 95% CI 1.03-5.32).

Conclusions

This study could not demonstrate any differences in thrombophilic markers between CVT patients and DVT/PE patients aged between 15 and 50 years, while the frequency of some transient risk factors was different. CVT was relatively more common in women and hormonal factors may predispose to CVT compared to DVT/PE, while trauma, immobilization and surgery may be less important in the pathophysiology of CVT.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare manifestation of venous thromboembolism (VTE). The estimated annual incidence is 3 to 5 per million, mainly affecting young women[1,2]. In contrast, deep venous thrombosis of the legs and/or pulmonary embolism (DVT/PE) is much more common and a disease of aging. The annual incidence of DVT/PE before the age of 50 years is 50-100 per 100,000, exponentially rising till around 800 per 100,000 at 80 years[3]. VTE is associated with many hereditary and acquired factors, of which some are age-dependent. It remains unclear why VTE less often manifests in the brain than in the legs. Age-dependent differences in risk profile between CVT and DVT/PE may play a role in the pathogenesis. The few studies that exist so far, which compared risk factors between CVT and DVT/PE, were without regard to age[4-6]. The heterogeneity for age may have influenced the results of these studies. The aim of this study was to compare risk factors in a uniform age group of CVT and DVT/PE patients aged between 15 and 50 years, in search for differences in frequency of risk factors for CVT in comparison to DVT/PE.

MATERIALS AND METHODS

Patients

The CVT series consisted of 79 patients aged between 15 and 50 years who were selected from a CVT registry of 98 consecutive patients aged 15 years or older, and were diagnosed in the University Medical Centre Groningen between 1994 and 2008[7,8]. The DVT/PE series consisted of 173 patients aged between 15 and 50 years who were selected from a DVT/PE registry of consecutive patients diagnosed in the same centre between 2000 and 2006. Thrombophilia tests were performed as previously described[9].

Statistical analysis

The frequency of thrombophilic markers and clinical risk factors for CVT and DVT/PE patients were compared using the Chi-square test or Fisher's exact test where appropriate. Age was compared using the Mann-Whitney U test. Multivariable logistic regression analysis was used to investigate the independent relation between the risk factors and the site of thrombosis. Variables with $p < 0.10$ in the univariate analysis were selected for multivariable analysis. A 2-sided p value < 0.05 was considered as statistically significant. All statistical analyses were performed with SPSS 16.0 for Windows, Chicago, USA.

RESULTS

Characteristics of the 79 CVT patients and 173 DVT/PE are presented in Table 5.1. CVT patients were younger (median age 30 versus 42 years; $p < 0.001$) and more often female (82% versus 52%; $p < 0.001$). There were no significant differences in thrombophilic markers between both groups. In women, oral contraceptive (OC) use and pregnancy/puerperium were more often present in CVT than in DVT/PE (63% versus 45%; $p = 0.031$ and 18% versus 8%; $p = 0.051$ respectively). Trauma, immobilization or surgery was less often found in CVT patients (6% versus 21%; $p = 0.008$).

Table 5.1 Characteristics of 79 CVT patients and 173 DVT/PE patients

Characteristic (missing values CVT-DVT/PE)[a]	CVT n (%)[a]	DVT/PE n (%)[a]	p
Median age (years) (range)	30.0 (16-50)	42.0 (17-50)	<0.001*
Women	65 (82)	90 (52)	<0.001*
Recurrent venous thromboembolism	19 (24)	51 (29)	0.372
Thrombophilia testing			
Factor V Leiden (7-15)	14 (19)	42 (27)	0.320
Heterozygous	14 (19)	38 (24)	
Homozygous	0 (0)	4 (3)	
Prothrombin G20210A (8-16)	3 (4)	4 (3)	
Heterozygous	3 (4)	4 (3)	0.680
Homozygous	0 (0)	0 (0)	
Protein C deficiency (8-21)	3 (4)	6 (4)	0.922
Protein S deficiency (7-19)	0 (0)	2 (1)	1.000
Antithrombin deficiency (6-11)	0 (0)	1 (1)	1.000
Factor VIII > 1.50 U/ml (15-30)	33 (52)	68 (48)	0.594
Lupus anticoagulant (18-41)	2 (3)	1 (1)	0.235
Acquired risk factors			
Hormonal factor (0-2)	53 (82[b])	47 (53[b])	<0.001*,[b]
Oral contraceptives	41 (63[b])	40 (45[b])	0.031*,[b]
Hormonal replacement therapy	0 (0[b])	0 (0[b])	
Pregnancy/puerperium	12 (18[b])	7 (8[b])	0.051[b]
Trauma/immobilization/surgery (0-2)	5 (6)	36 (21)	0.003*
ENT/CNS infection	10 (13)		
Associated diseases			
Malignancy (0-2)	11 (14)	14 (8)	0.160
Immune disease (0-1)	9 (11)	21 (12)	0.853
Not any factor (2-1)	5 (6)	22 (13)	0.140

CVT = cerebral venous thrombosis; DVT/PE = deep vein thrombosis and/or pulmonary embolism; ENT = ear/nose/throat; CNS = central nervous system
[a]Unless otherwise indicated
[b]Values among women
* $p < 0.05$

Multivariable analysis

In all patients, a logistic regression analysis was performed with 'age', 'sex', 'trauma, immobilization or surgery' (Table 5.2A). 'Hormonal factor' only relates to women and an additional logistic regression analysis restricted to women with 'hormonal factor', 'age' and 'trauma, immobilization and surgery' was performed. Since 'OC use' and 'pregnancy/puerperium' are correlated, the overlapping variable 'any hormonal factor' was entered in the model (Table 5.2B). Trauma, immobilization or surgery were independently less associated with CVT than with DVT/PE (odds ratio (OR) 0.29; 95% confidence interval (CI) 0.10-0.82; $p = 0.020$). In women, hormonal factors were independently more strongly associated with CVT than DVT/PE (OR 2.34; 95% CI 1.03-5.32; $p = 0.043$).

Table 5.2 Multivariable analysis: association of risk factors with site of thrombosis (CVT compared to DVT/PE)

	Variables	OR[a]	95% CI	p
A	Age	0.92	0.89-0.95	<0.001*
	Male	0.34	0.17-0.69	0.002*
	Trauma/ immobilization/ surgery	0.29	0.10-0.82	0.020*
B	Age	0.93	0.90-0.97	<0.001*
	Trauma/ immobilization/ surgery	0.43	0.13-1.36	0.151
	Hormonal factor	2.34	1.03-5.32	0.043*

A: Logistic regression analysis in all patients.
B: Logistic regression analysis restricted to women
CVT = cerebral venous thrombosis; DVT/PE = deep vein thrombosis and/or pulmonary embolism; OR = odds ratio; CI = confidence interval
[a] CVT compared to DVT/PE
* $p < 0.05$;

DISCUSSION

This is the first study which compared risk factors in a uniform age group of CVT and DVT/PE patients aged between 15 and 50 years. There were not any differences found in thrombophilic markers between CVT and DVT/PE patients. However, the frequency of some transient risk factors between the groups was different. CVT occurred more frequently in women, secondary to hormonal factors and less often secondary to trauma, immobilization or surgery compared to DVT/PE.

There are a few other studies which compared risk factors in CVT and DVT/PE patients. None of these studies focused on patients aged younger than 50 years[4-6]. As in this study, one study found no differences in thrombophilic markers[6]. Two studies reported a lower frequency of factor V Leiden mutation in CVT patients[4,5]. One study reported a lower frequency of protein C deficiency and a higher frequency of the prothrombin G20210A mutation in the CVT group[4]. These variable results suggest that there is no specific thrombophilic marker which predispose to CVT compared to DVT/PE. All studies reported a higher frequency of OC use and a lower frequency of surgery and/or immobilization in CVT patients[4-6]. Some acquired risk factors like OC use and pregnancy are largely restricted to patients younger than 50 years, while immobilization may be more important in older

patients. Nevertheless, this study in a uniform age group confirms the higher frequency of OC use and the lower frequency of surgery or immobilization in CVT compared to DVT/PE.
A possible explanation for the differences in the frequency of some risk factors in CVT compared to DVT/PE may be found in anatomical factors. The cerebral veins have no valves, which is in contrast to the deep veins of the lower legs. The valves may induce stasis of blood, which may be enhanced by gravity and immobilization, and lead to thrombus formation. Another explanation may be a difference in expression of anticoagulants and procoagulants of the local endothelium in cerebral veins. This may result in a site-specific thrombotic balance, which may interact in a different way with risk factors like hormonal influences[10].
The study has limitations. Firstly, the study population is small and this limits statistical analysis. The results have to be interpreted with caution and needs confirmation before definitive conclusions can be drawn. Secondly, the patients were retrospectively selected from a registry of consecutive patients and not all patients had complete thrombophilia testing. Furthermore, some thrombophilia tests may be less reliable due to confounding factors such as medication and comorbidity[11]. This was tried to reduce by standardization and when possible with repeated measurements[9].

In conclusion, this study could not demonstrate any differences in thrombophilic markers between CVT patients and DVT/PE patients aged between 15 and 50 years, while the frequency of some transient risk factors was different. Though CVT occurs less often than DVT/PE, it is relatively more common in women and hormonal factors may predispose to CVT compared to DVT/PE, while trauma, immobilization and surgery may be less important in the pathophysiology of CVT. Further investigating is needed to confirm the results and explain site-specific thrombosis.

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THROMBOELASTOGRAPHY IN PATIENTS WITH CEREBRAL VENOUS THROMBOSIS

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ABSTRACT

Background and purpose

Cerebral venous thrombosis (CVT) is a rare presentation of venous thrombosis and has been associated with many conditions. In about 15% no risk factor can be identified. The aim of this study was to assess the clot formation by thromboelastography (TEG) in patients with a history of CVT compared with healthy controls.

Materials and Methods

TEG analysis was performed on recalcified blood samples of 19 CVT patients from a single centre cohort and 1:1 sex/age (+/- 3 years) matched controls. Four TEG parameters were monitored: reaction time (r) to clot initiation, time to reach a 20 mm level of clot formation (K), slope angle alpha from r to K (α) and maximum vertical amplitude (MA). Patients were tested for thrombophilic markers, including deficiencies of antithrombin, protein C and protein S, factor V Leiden mutation, prothrombin G20210A mutation, lupus anticoagulant and high factor VIII levels (> 1.50 U/ml).

Results

Thrombophilia testing identified a thrombophilic marker in 11 patients (58%). Sixteen patients (84%) had one or more transient risk factors. There were no significant differences in TEG parameters between CVT patients and controls, neither between the subgroup of patients with a thrombophilic marker and controls. Seven of all patients (37%), including 5 patients with abnormal thrombophilia testing, and 5 controls (26%) had one or more TEG hypercoagulable parameters.

Conclusions

A persistent hypercoagulable state which could have predisposed to venous thrombosis in CVT patients and in the subgroup of patients with a thrombophilic marker could not be demonstrated by TEG.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare presentation of venous thrombosis with an annual incidence of 3 to 5 per million in the general population[1,2]. Many genetic and acquired conditions, either local or systemic, have been associated with CVT. If there is a combination of associated factors, the risk for venous thrombosis may be higher. The high prevalence of some risk factors and the low prevalence of CVT suggest that some risk factors just have an attributive effect in already predisposed patients[3]. Furthermore, in about 15% of the patients, no risk factor can be identified. By virtue of their presenting thrombosis, these patients may be considered 'thrombophilic' at that time. It is also unclear why a thrombus is more often located in the deep veins of the legs than in the brain, a finding that is not fully explained by local factors. Other unknown local or systemic factors might play a role[4].

Thromboelastography (TEG) is performed on whole blood and monitors haemostasis as a dynamic process, evaluating both the process of clot formation, stabilization and clot lysis[5-7]. TEG has been shown to provide additional information on the haemostatic process in comparison with conventional laboratory tests[8,9].

The aim of this study was to assess TEG in patients with a history of CVT compared with healthy controls.

MATERIALS AND METHODS

Subjects

Data were derived from a single centre data base of consecutive symptomatic CVT patients aged 15 years and older who were admitted to the University Medical Centre Groningen between January 1997 and July 2007. CVT had to be confirmed by magnetic resonance imaging with venography, computed tomography with venography, digital subtraction angiography or surgery, according to the current diagnostic criteria[10]. The following information was registered: demographic data, medical history, symptoms and signs, time to diagnosis, imaging modality, location of the thrombus, (haemorrhagic) parenchymal lesions, treatment, course, laboratory tests for thrombophilia, exposure to transient risk factors within 3 months prior to CVT and comorbidity. Laboratory tests for thrombophilia included deficiencies of antithrombin, protein C and protein S, factor V Leiden mutation (FV Leiden), prothrombin G20210A mutation (prothrombin G20210A), lupus anticoagulant (LAC) and increased plasma levels of factor VIII (FVIII:C) (> 1.50 U/ml). These were performed at least 3 months after CVT, while the patient did not use oral contraceptives or vitamin K antagonists.

After informed consent was obtained, 19 CVT patients were included, who were 1:1 matched for sex and age (+/- 3 years) with healthy volunteers[11].

Thromboelastography

TEG was performed with a 5000 series TEG® analyser (Haemoscope Corp., I1, USA). Blood for TEG assessment was collected via antecubital vein puncture with a 20G needle into a 3.5 ml tube containing 3.2% sodium citrate. The first 4 ml of blood was discarded to avoid contamination with tissue thromboplastin. After 60-70 minutes, blood samples for analysis were prepared by adding 20 µl $CaCl_2$ 0.2M to 340 µl of the citrated whole blood at a total volume of 360 µl in a plastic disposable cup. The following 4 standard parameters were determined at 37°C: reaction time (r, min) to clot initiation, kinetic time to reach a 20 mm level of clot formation (K, min), slope angle alpha (α, degrees) from r to K and maximum vertical amplitude (MA, mm). The reference ranges for recalcified blood were used, as were given by the manufacturer of the TEG analyser. A value of a parameter outside the reference range of the TEG of recalcified blood was defined as a hypercoagulable parameter (below lower limit for r and K; above upper limit for α and MA).

Statistical analysis

Group A and group B were defined. Group A contained all CVT patients, group B consisted of the subgroup of patients with abnormal results of thrombophilia tests. Data was described as mean ± standard deviation (SD). TEG parameters were compared using nonparametric Mann-Whitney U tests between the mean values of patients and controls and Wilcoxon matched pairs signed rank sum tests between the paired values in group A and B. A two-sided p-value < 0.05 was considered as statistically significant. Statistical analysis was performed with SPSS version 14.0 for Windows.

RESULTS

The baseline characteristics and TEG results of the 19 patients (15 women (79%)) and the matched controls are presented in Table 6.1. The mean age at time of TEG analysis was 36 years (median 32; range 18-55). The mean time between CVT and TEG was 56 months (median 45; range 3-119). Fourteen patients (74%) had multiple risk factors and in 2 patients (11%), no associated factor was identified. Sixteen patients (84%) had one or more transient factor. Three patients (16%) had a local risk factor (meningitis, ear/nose/throat infection and head injury, respectively).

Group B consisted of 11 patients (58%) who had abnormal results of thrombophilia tests (6 patients with elevated FVIII:C, 3 patients with FV Leiden, 1 patient with prothrombin G20210A, 1 patient with LAC, 0 patients with deficiencies of antithrombin, protein C and protein S). Ten of these patients (91%) had an additional risk factor.

There were no significant differences in the mean and the paired values of the TEG parameters between patients in group A and B and their controls (Table 6.2). Seven of all CVT patients (37%), including 5 patients from group B, had one or more TEG hypercoagulable parameters (4 patients with shortened r, 1 patient with shortened K, 3 patients with increased α and 4 patients with increased MA). Five controls (26%) had a hypercoagulable parameter (1 control with shortened r

Table 6.1 Characteristics and TEG parameters of 19 CVT patients and 19 sex/age matched controls

	Sex	Age (yr)	D-T (mth)	Risk factors	TEG parameters CVT patients				TEG parameters controls			
					r	K	α	MA	r co	K co	α co	MA co
				Reference range	9-27	2-9	22-58	44-64	9-27	2-9	22-58	44-64
1	F	23	42	OC, CU, FVIII ↑	**8.8**	2.7	52.0	59.8	9.7	5.2	36.6	59.1
2	F	41	83	Pregnancy, FVIII ↑	11.6	3.7	44.0	58.2	**8.4**	3,7	47,5	60,4
3	F	39	108	OC, FVIII ↑	**3.2**	2.8	**58.2**	51.6	12	3	55.9	**67.1**
4	F	25	106	FV Leiden, puerperium	9.8	3.9	44.7	59.9	9.2	2.5	39.7	**70.2**
5	F	30	15	FVIII ↑	**8.1**	2.3	57.9	**68.0**	9.3	5.3	40.2	57.3
6	M	47	66	FII G20210A, ENT inf	10.8	**1.9**	**62.5**	**69.0**	19.3	6.7	30.3	49.3
7	F	26	30	FV Leiden, OC	14.2	5.8	34.8	51.5	10.6	4.8	39.9	62.2
8	F	28	31	Puerperium, FVIII ↑	10.2	4.8	39.1	49.5	12.3	3.4	52.2	**69.2**
9	F	22	28	OC, APA syndrome	14.1	2.6	55.7	**65.0**	11.8	5.5	37.2	57.8
10	F	52	119	FV Leiden, OC	10.5	4.9	25.4	61.8	12.1	3.3	53.3	**66.1**
11	M	55	3	Head injury, FVIII ↑	9.8	4.9	39.8	56.2	12.0	4.0	31.3	55.0
Mean B		36	57		10.1	3.7	46.7	59.1	11.5	4.3	42.2	61.2
SD B		11	41		3.0	1.3	11.5	6.6	2.9	1.3	8.8	6.5
12	M	42	18	Meningitis	24.5	*11.6*	*18.4*	48.0	18.6	*11.8*	*17.8*	48.5
13	F	53	92	None identified	10.2	2.5	47.1	58.1	10.9	4.8	37.3	61.0
14	F	32	60	OC, malignancy	11.3	2.7	52.6	63.7	10,1	4,0	44,2	57,3
15	F	31	45	OC, SLE	18.3	6.3	30.0	61.4	12.9	5.1	36.1	56.8
16	F	35	10	OC, erythema nodosum	**7.8**	2.1	**61.1**	62.2	11.6	4.5	41.0	60.1
17	F	27	94	OC	10.6	4.6	40.2	55.3	13.3	5.3	36.8	55.5
18	M	51	100	None identified	11.1	4.8	37.9	59.8	11.9	5.8	33.1	61.4
19	F	18	16	Malignancy, surgery	9.8	2.0	38.0	**66.8**	10.2	5.0	37.2	60.8
Mean A		36	56		11.3	4.0	44.2	59.3	11.9	4.8	39.3	59.7
SD A		11	39		4.4	2.3	12.3	6.1	2.8	2.0	8.9	5.8

M = male; F = female; Age (yr) = age at time of TEG analysis (years); D-T (mth) = time between diagnosis and thromboelastography (months); TEG = thromboelastography; CVT = cerebral venous thrombosis; Reference range = reference range TEG parameters of recalcified blood; r = reaction time to clot initiation; K = time to reach a 20 mm level of clot formation; α = slope angle alpha from r to K; MA = maximum vertical amplitude; co = controls; SD = standard deviation; OC = oral contraceptive; CU = colitis ulcerosa; FVIII ↑ = increased plasma levels of factor VIII (> 1.50 U/ml), FV Leiden = factor V Leiden mutation; FII G20210A = prothrombin G20210A mutation; ENT infection = ear/nose/throat infection; APA = antiphospholipid antibodies; SLE = systemic lupus erythematosus

In bold: hypercoagulable

In italics: hypocoagulable

A: group A: all 19 CVT patients (1-19)

B: group B: subgroup of 11 CVT patients (1-11) with deficiencies of antithrombin, protein C and protein S, FV Leiden, prothrombin G20210A, APA or FVIII ↑

Table 6.2 Mann-Whitney U and Wilcoxon test between thromboelastography parameters of 19 CVT patients and 19 controls

TEG Parameter	r	K	α	MA
Test	p	p	p	p
Mann-Whitney U test group A	0.21	0.07	0.14	0.94
Wilcoxon matched signed rank sum test	0.53	0.12	0.09	0.94
Mann-Whitney U test group B	0.38	0.25	0.31	0.49
Wilcoxon matched signed rank sum test	0.48	0.44	0.33	0.53

CVT = cerebral venous thrombosis; TEG = thromboelastography; r = reaction time to clot initiation; K = time to reach a 20 mm level of clot formation; α = slope angle alpha from r to K; MA = maximum vertical amplitude
Group A: 19 CVT patients
Group B: 11 CVT patients with deficiencies of antithrombin, protein C and protein S, factor V Leiden, prothrombin G20210A mutation, antiphospholipid antibodies or increased plasma levels of factor VIII (> 1.50 U/ml);

and 4 controls with increased MA). Two patients without identified risk factor and 2 patients with a single acquired risk factor had a normal TEG. In group B, the patient with prothrombin G20210A had 3 TEG hypercoagulable parameters and none of the patients with FV Leiden had hypercoagulable parameters.

DISCUSSION

There were no significant differences in TEG variables between CVT patients and healthy controls. Also, there were no significant differences in the subgroup analysis of patients with a thrombophilic marker. A persistent hypercoagulable state in patients with a history of CVT could not be demonstrated.

Previous studies on the aetiology of CVT reported that thrombophilic markers as FV Leiden, prothrombin G20210A, elevated FVIII levels and antiphospholipid antibodies were more frequently observed in CVT patients than in the general population, suggesting a predisposition to venous thrombosis[12-18]. One study reported furthermore no differences in the prevalence of FV Leiden and prothrombin G20210A between 40 CVT patients and 80 patients with deep vein thrombosis or pulmonary embolism and another study found no differences in the results of thrombophilia tests between 63 CVT patients and 209 patients with deep vein thrombosis or pulmonary embolism[4,19]. There is little known about the relation between venous thrombosis and the TEG. In a study of 87 patients with a personal or family history of venous thrombosis, thrombophilia tests (deficiencies of antithrombin, protein C and protein S, FV Leiden, prothrombin G20210A, antiphospholipid antibodies and increased plasma levels of factor VIII) and TEG were performed [9]. The reference ranges were established using 19 healthy controls. A hypercoagulable TEG parameter was demonstrated in 39 patients (45%) of which 17 had a thrombophilic trait. On the other hand, of 30 patients (34%) with established thrombophilia, 17 had a hypercoagulable TEG. The effect of genetic thrombophilic factors on TEG was also studied in 588 pregnant women. This study reported a significant correlation of TEG parameters with antithrombin levels, but found no relationship between TEG variables and levels of protein C, protein S, FV Leiden, prothrombin G20210A or pregnancy complication[20]. The results of these studies suggest that some patients have a prothrombotic state, although its physiological basis is not clarified, and that TEG may be a useful adjunctive test, but cannot reliable identify genetic thrombophilia. In this study, the only patient with prothrombin G20210A had a hypercoagulable TEG, while none of the 3 patients with FV Leiden showed a hypercoagulable TEG.

The study has limitations. Firstly, the study population was small and consisted of 19 CVT patients with heterogeneous risk factors. Subgroup analysis was only performed in patients with abnormal thrombophilia testing. It would be of interest to analyse more homogeneous subgroups of CVT patients and to subdivide the patients into normal-abnormal thrombophilia tests with presence-absence of an additional or local risk factor and its interaction to TEG results. The sample size of the study was too small to divide into reliable subgroups. Because CVT is a rare disease and risk factors are so many, it will take a long time to perform such a study. Secondly, TEG analysis was not performed in the acute phase of CVT and the follow-up ranged from 3 to 119 months. Acute thrombosis can influence TEG results and some risk factors at the time of CVT may no longer exist at time of TEG analysis[5-7]. However, it was the intention to investigate whether CVT patients had a persistent hypercoagulable state and it was not the aim to investigate TEG abnormalities in the acute phase. Thirdly, recalcified samples were used for practical reasons. Although it has been shown that recalcification can influence TEG parameters, this effect remained stable between 30 minutes and up to 8 hours after collection[21-23]. It is, however, unknown what the effect of recalcification is on samples from (probably) hypercoagulable patients, so an influence of the use of recalcified blood samples on the results in this study could not be excluded. The reference ranges for recalcified blood were used, as were given by the manufacturer of the TEG analyzer. A substantial number of both CVT patients and healthy controls had a value outside this reference range. This may suggest that this range is not accurate, but this did not influence the performed analysis in which patients were compared with healthy controls.

In summary, a hypercoagulable state which could have predisposed to venous thrombosis in patients with a history of CVT and in the subgroup of patients with a thrombophilic marker could not be established by TEG. Further investigation about the aetiology of CVT and the (added) value of the TEG in screening for thrombophilia is required.

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7

JAK2-V617F MUTATION IN CEREBRAL VENOUS THROMBOSIS

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ABSTRACT

Background and purpose

Cerebral venous thrombosis (CVT) is an unusual manifestation of thrombosis. The *Janus kinase 2* V617F (*JAK2*-V617F) mutation is frequently found in some forms of myeloproliferative disorders (MPD). Splanchnic vein thrombosis (SVT) is another unusual site of thrombosis and has been associated with the *JAK2*-V617F mutation in the absence of MPD. The association of the *JAK2*-V617F mutation irrespective of MPD and cerebral venous thrombosis (CVT) is not clear. The aim of this study was to assess the frequency of the *JAK2*-V617F mutation in a series of CVT patients and to perform a systematic review of the literature.

Materials and Methods

DNA samples of 59 CVT patients were analysed for the presence of the *JAK2*-V617F mutation. A literature search was performed using PubMed and Embase.

Results

In the CVT patient series, the *JAK2*-V617F mutation was detected in 1 of the 2 patients with essential thrombocythemia and in the one patient with polycythemia vera. The *JAK2*-V617F mutation was not detected in 56 patients without overt MPD. Review of the literature revealed 7 studies with 237 CVT patients without MPD. The frequency of the *JAK2*-V617F mutation ranged from 0 to 14%. Most studies did not detect the mutation in any CVT patient without MPD.

Conclusions

This study suggests that the *JAK2*-V617F mutation can be found in CVT patients with known MPD, but there is no association between the *JAK2*-V617F mutation and CVT in patients without overt MPD, in contrast to SVT. Routine screening of the *JAK2*-V617F mutation in CVT patients without overt MPD does not seem useful.

INTRODUCTION

Cerebral venous thrombosis (CVT) is an uncommon manifestation of venous thromboembolism (VTE) with an annual incidence of 3 to 5 per million in the general population[1,2]. The *Janus kinase 2* V617F (*JAK2*-V617F) mutation is frequently found in patients with Philadelphia negative myeloproliferative disorders (MPD). MPD is often complicated by thrombosis at several locations and has also been described in CVT[1-5]. Splanchnic vein thrombosis (SVT) is another unusual site of thrombosis and relatively common in patients with MPD and the *JAK2*-V617F mutation. Furthermore, the *JAK2*-V617F mutation has been found in SVT patients without overt MPD[3,6]. Hence, the *JAK2*-V617F mutation may be associated with thrombosis at an unusual site, irrespective of the presence of MPD. In that case, the *JAK2*-V617F mutation may also be associated with CVT in the absence of MPD. However, this association is not clear, despite recently published studies[7-13].
The aim of this study was to assess the frequency of the *JAK2*-V617F mutation in a series of CVT patients and to perform a systematic review of the literature.

MATERIAL AND METHODS

Patients

The series consisted of 59 CVT patients from an ongoing CVT registry of the University Medical Centre Groningen from January 1994 which has been described previously and of whom DNA specimens were available for analysis[14]. CVT was diagnosed according to the current diagnostic criteria and had to be confirmed by magnetic resonance imaging with venography, computed tomography with venography, digital subtraction angiography, surgery or autopsy[15]. The following information was registered: demographic data, medical history, symptoms and signs, time to diagnosis, imaging modality, location of the thrombus, (haemorrhagic) parenchymal lesions, treatment, course, results of thrombophilia testing, risk factors (within 3 months prior to CVT) and comorbidity. Thrombophilia tests included deficiencies of antithrombin, protein C, protein S, factor V Leiden mutation, the prothrombin G20210A mutation, lupus anticoagulant and factor VIII levels higher than 1.50 U/ml, performed as previously described[16].

JAK2-V617F analysis

Genomic DNA was extracted by using Qiagen Blood Mini kit according to the manufacturer's instructions. *JAK2*-V617F DNA was analysed by a real time polymerase chain reaction (qRT-PCR) (ABI Prism® 7500 Real Time PCR System, Applied Biosystems, Foster City CA, USA) as previously described[17]. The forward primer AAGCTTTCTCACAAGCATTTGGTTT, the reverse primer AGAAAGGCATTAGAAAGCCTGTAGTT and the *JAK2*-V617F probe FAM-TCCACAGAAACATAC-BHQ were used. Probes were obtained from Applied Biosystems and primers from Invitrogen Ltd (3 Fountain Drive, Paisley, UK). The amount of *JAK2*-V617F DNA was calculated using a calibration curve constructed with twofold serially diluted genomic DNA from the *JAK2*-V617F positive HEL cell line into DNA from the *JAK2* wild-type HL-60 cell line[18]. The assay was capable of detecting 0.8% *JAK2*-V617F DNA.

Literature search

A literature search was performed using PubMed and Embase. A combination of the key words '*JAK2*' or '*JAK2*-V617F' and 'cerebral venous thrombosis' or 'sinus thrombosis' was used without any restriction. All references of the included studies were additionally checked for bibliographical data of all included publications for further studies.

RESULTS

Table 7.1 Characteristics of 59 CVT patients

Characteristic (missing value[a])	n (%)[a]
Mean age diagnosis (years) (IQR)	33.0 (23-43)
Female	44 (75)
Mean follow-up (months) (IQR)	20 (19-24)
Venous thromboembolism	13 (22)
History	9(15)
Follow up	6(10)
Thrombophilia testing	
Antithrombin deficiency	0 (0)
Protein C deficiency	3 (5)
Protein S deficiency (3)	0 (0)
Factor V Leiden	7 (12)
Prothrombin G20210A mutation	0 (0)
Factor VIII higher than 1.50 U/ml (15)	22 (50)
Lupus anticoagulant (14)	2 (4)
JAK2-V617F mutation	2 (3)[b,c]
Acquired risk factors	
Oral contraceptives/HRT	24 (55)[d]
Pregnancy/ puerperium	10 (23)[d]
ENT/CNS infection	9 (15)
Trauma/immobilization/surgery	7 (12)
Associated diseases[e]	12 (20)
Essential thrombocythemia	2 (3)[b]
Polycythemia vera	1 (2)[c]
Primary myelofibrosis	0 (0)
No risk factor	9 (15)

CVT = cerebral venous thrombosis; IQR = interquartile range; *JAK2*-V617F = *Janus kinase2* V617F mutation; HRT = hormone replacement therapy; ENT = ear/nose/throat; CNS = central nervous system

[a] Unless otherwise indicated

[b] *JAK2*-V617F mutation in 1 out of the 2 patients with essential thrombocythemia

[c] *JAK2*-V617F mutation in the one patient with polycythemia vera

[d] Percentage among women

[e] Including malignancy, haematological, (auto)immune disorders.

Patients

Characteristics of the 59 patients are presented in Table 7.1. Three patients (5%) had MPD at time of CVT. The *JAK2*-V617F mutation was detected in 1 of the 2 patients with known essential thrombocythemia and in the one patient with known polycythemia vera.

The *JAK2*-V617F mutation was not detected in the 56 CVT patients without overt MPD at time of CVT. During follow-up (median time 24 months), none of these patients developed MPD.

Literature search

With the search terms, PubMed and Embase yielded 9 articles. Of these, 5 articles studied the *JAK2*-V617F mutation in cerebral venous thrombosis irrespective of MPD and were included. Four articles did not study the topic of interest and were excluded. Additionally, 2 studies were included by checking references and related articles (Table 7.2). The frequency of the *JAK2*-V617F mutation in patients without overt MPD ranged from 0 to 14%[7-13]. In 2 studies, the *JAK2*-V617F mutation was detected in 3 of the 48 CVT patients (6%)[9] and 1 of the 7 CVT patients (14%)[11] without overt MPD at time of CVT. Four other studies found the *JAK2*-V617F mutation in only 1 out of 87 CVT patients (1%)[12] and none out of 6[7], 45[10] and 44[13] CVT patients without overt MPD, respectively. Limited follow-up data reported no development of MPD in the CVT patients with the *JAK2*-V617F mutation without overt MPD at time of CVT. One study reported the *JAK2*-V617F mutation in 3 of the 4 patients with overt MPD at time of CVT[8].

Table 7.2 Studies about the *JAK2*-V617F mutation in CVT patients without MPD

Study	n	*JAK2*-V617F n (%)
Remacha et al[7]	6	0 (0)
De Stefano et al[8,9,a]	48	3 (6)[d]
Colaizzo et al[10]	45	0 (0)
Pardanani et al[11]	7	1 (14)[e]
Bellucci et al[12]	87	1 (1)[f]
Xavier et al[13;b]	44	0 (0)
This study[c]	56	0 (0)

JAK2-V617F = *Janus kinase 2* V617F mutation; CVT = cerebral venous thrombosis; MPD = myeloproliferative disorder

[a] Study did not include CVT patients with malignancy and consisted of 52 CVT patients including 4 CVT patients with overt MPD of whom 3 with *JAK2*-V617F

[b] Study did not include CVT patients with infection, trauma, malignancy or autoimmune disease

[c] Study consisted of 59 CVT patients including 3 CVT patients with overt MPD of whom 2 with *JAK2*-V617F

[d] In 1 patient platelet count rises during follow-up

[e] Patient with recurrent pulmonary embolism and CVT during follow-up

[f] No follow-up

DISCUSSION

In the patient series, the *JAK2*-V617F mutation was detected in 1 of the 2 patients with known essential thrombocythemia and in the one patient with known polycythemia vera. The *JAK2*-V617F mutation was not found in 56 CVT patients without overt MPD at time of CVT or during follow-up. Other studies reported *JAK2*-V617F frequencies between 0 and 14% in CVT patients without MPD. However, most of these studies did not detect the mutation in any CVT patients without overt MPD, which is confirmed by the results of this series[7-13].

The *JAK2*-V617F mutation may result in abnormal haematopoiesis and has been found in about 90% of the patients with polycythemia vera and in about half of the patients with essential thrombocythemia and primary myelofibrosis[4,5]. Thrombosis at several locations is a major complication of MPD and the *JAK2*-V617F mutation may increase the risk of thrombosis in MPD patients[3,6]. SVT accounts for a relatively high proportion in patients with MPD and has also been found in 0 to 47% of SVT patients without overt MPD at time of SVT or during follow-up[5,6]. In contrast, there may be no association with the more usual sites of VTE and the *JAK2*-V617F mutation in the absence of MPD. Studies reported frequencies of the *JAK2*-V6717F mutation between 0 and 1% in patients with deep venous thrombosis or pulmonary embolism[7,10,11,19]. This study suggests, furthermore, that CVT as unusual site is not associated with the *JAK2*-V617F mutation irrespective of MPD, in contrast to SVT.
The study has limitations. Firstly, the patient series was relatively small and consisted of CVT patients with heterogeneous acquired or genetic factors. Secondly, the literature search only revealed 7 studies and follow-up information was limited.

In conclusion, the *JAK2*-V617F mutation can be found in CVT patients with known MPD, but the frequency of the *JAK2*-V617F mutation in CVT patients without overt MPD is very low. This suggests that the *JAK2*-V617F mutation in the absence of a known MPD is not associated with CVT, in contrast to the suggested association with SVT. Therefore screening for the *JAK2*-V617F mutation in CVT patients without MPD does not seem useful.

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8

SUMMARY

This thesis describes a number of clinical and haematological aspects of cerebral venous thrombosis (CVT).

Chapter 1 provides a general introduction of CVT and describes the aims and outlines of the thesis. CVT is a rare disease with an estimated annual incidence of 3 to 5 per million. It is most common in young women aged between 20 to 35 years. It accounts for only 0.5-1.0% of all strokes and is an uncommon site of venous thromboembolism (VTE). The clinical presentation is highly variable. The most common symptoms are headache, focal neurological deficits, seizures and disturbance of consciousness. Many hereditary and acquired risk factors have been associated with CVT. In about 15%, no risk factor can be identified. There may be other as yet unidentified factors that cause CVT. Diagnosis nowadays is made by neuroimaging. Current treatment is based on 'best evidence available' and consists of anticoagulation for 3 to 12 months, depending on the underlying cause, in combination with symptomatic treatment of seizures and raised intracranial pressure. The prognosis of CVT is generally good. About 80% of the patients regain functional independence. However, these patients may experience long-term sequelae. Although the knowledge about CVT has been growing during the last decades, further investigation of clinical and haematological aspects is required.

This thesis aims to answer the following questions:

1. Is it possible to develop a score which could help to predict outcome in CVT patients? (chapter 3)
2. Do CVT patients with a good outcome experience long-term sequelae with impact on daily life? (chapter 4)
3. Are there differences in risk factors between CVT patients and patients with deep venous thrombosis and/or pulmonary embolism (DVT/PE) aged between 15 and 50 years which could give more insight in site-specific thrombosis? (chapter 5)
4. Could thromboelastography (TEG) demonstrate a persistent hypercoagulable state in patients with a history of CVT? (chapter 6)
5. Is the *Janus kinase 2* V617F (*JAK2*-V617F) mutation associated with CVT, irrespective of the presence of a myeloproliferative disorder (MPD)? (chapter 7)

In chapter 2, the CVT cohort of the University Medical Centre of Groningen (UMCG) is described. The UMCG-CVT cohort consisted of 98 patients who were investigated in the UMCG between January 1994 and March 2009. Median age was 34.5 years (range 16-81) and 77 patients (79%) were female. Demographics of the patients, medical and familial history with special attention to VTE, clinical presentation, brain imaging findings, treatment modus, results of thrombophilia tests, exposure to transient risk factors, comorbidity, clinical outcome and follow-up data about the recurrence of thrombosis and seizures were registered.

Outcome was assessed with the modified Rankin scale (mRS). Eighty patients (82%) had a mRS score ≤ 2 (functionally independent outcome). Six patients (6%) died. In 12 patients (13%), no risk factor for CVT was identified. In the last paragraph of chapter 2, the main characteristics of other CVT cohorts found in the literature are given, with special attention to the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) published in 2004. The ISCVT of 624 patients is the largest prospective observational study published so far. The characteristics of the UMCG-CVT cohort are comparable with the ISCVT cohort and other cohorts.

Chapter 3 describes the development and validation of a score which may help to predict outcome in an individual patient and assist the clinician in decision making and informing patients and family. The score was based on the predictors of poor outcome identified in the ISCVT: age older than 37 years, male sex, mental status disorder, coma, intracranial haemorrhage, thrombosis of the deep cerebral venous system, central nervous system infection and malignancy. Poor outcome was defined as a mRS score > 2. The score was externally validated in 90 patients of the UMCG-CVT cohort. Using the optimal cut-off value, which was defined as the maximal sum of sensitivity and specificity, the score had a sensitivity of 88% and specificity of 70%. The predictive value for good outcome was 96%, whereas the predictive value for poor outcome was 39%.

Although functional outcome is good in the majority of CVT patients, these patients may encounter long-term sequelae. Chapter 4 describes a case-control study of the frequency of headache, depression, fatigue and concentration impairment and the impact on daily life and employment in a group of 44 CVT patients with a functionally independent outcome (mRS score ≤ 2) after CVT (median follow-up 63 months). About half of the CVT patients reported headache and 75% complained of concentration impairment. Depressive symptoms and fatigue were reported by one third of the patients. All sequelae were more often reported by patients than by controls. The sequelae had a negative impact on psychosocial functioning and interfered with employment resumption.

CVT is a rare disease mostly affecting young women. DVT/PE is much more common, especially in the elderly. It remains unclear why VTE less often manifests in the brain than in the legs. Age-related factors may play a role. Chapter 5 studied differences in risk factors between 79 CVT and 173 DVT/PE patients in a uniform age group between 15 and 50 years. The results of this study showed not any differences in thrombophilic markers. However, the frequency of some transient risk factors between the groups was different. CVT occurred more frequently in women, secondary to oral contraceptive use, pregnancy or puerperium and less often secondary to trauma, immobilization or surgery compared to DVT/PE patients.

Many factors have been associated with CVT, but in about 15% no risk factor can be identified. By virtue of their presenting thrombus, these patients may be considered as 'thrombophilic' at that time.

Chapter 6 studied the question whether a persistent hypercoagulable state could be demonstrated in patients with a history of CVT. In a case-control design, whole blood of 19 CVT patients and age/sex matched controls was analysed by TEG. TEG is a test on whole blood and monitors the haemostatic process. It measures time to clot initiation and speed and strength of clot formation. The study did not find any differences in the TEG variables between patients and controls, neither in the subgroup of patients with a thrombophilic marker. A persistent thrombophilic state in patients with a history of CVT could not be demonstrated by TEG.

Chapter 7 describes a study about the association between CVT and the *JAK2*-V617F mutation. The *JAK2*-V617F mutation is associated with some forms of MPD, of which thrombosis at several locations is a major complication. CVT and splanchnic vein thrombosis (SVT) are both rare manifestations of VTE. The *JAK2*-V617F mutation has been associated with SVT in patients with and without overt MPD. A patient series of the UMCG-CVT registry was investigated and a review of the literature was performed to investigate whether CVT, as an unusual manifestation of VTE, was also associated with the *JAK2*-V617F mutation, irrespective of MPD. In a series of 59 patients, the *JAK2*-V617F mutation was detected in 2 of the 3 patients with MPD (1 of the 2 patients with essential thrombocythemia and the one patient with polycythemia vera). The *JAK2*-V617F mutation was not detected in 56 patients without overt MPD. Review of the literature revealed 7 studies with 237 CVT patients without MPD. The frequency of the *JAK2*-V617F mutation ranged from 0 to 14%, but most studies did not detect the mutation in any CVT patient without MPD. These results suggest that the *JAK2*-V617F mutation is not associated with CVT in patients without MPD, in contrast to CVT patients with MPD.

In summary, the studies in this thesis answer the previous formulated questions:

1. A simple score to predict outcome in CVT patients was developed that accurately could predict good outcome but was less accurate in predicting poor outcome of CVT (chapter 3).
2. In the long-term, CVT patients with a functionally independent outcome often experienced headache, concentration impairment, fatigue and depression, all with a negative impact on daily life and work (chapter 4).
3. There were not any differences found in thrombophilic markers between CVT and DVT/PE patients aged between 15 and 50 years, while the frequency of some transient risk factors was different: hormonal factors were more associated with CVT, while trauma, immobilization and surgery were more associated with DVT/PE (chapter 5).
4. A persistent hypercoagulable state in patients with a history of CVT could not be demonstrated by TEG (chapter 6).
5. The *JAK2*-V617F mutation was not associated with CVT in patients without MPD (chapter 7).

9

GENERAL DISCUSSION

This chapter provides a general discussion of some of the results of this thesis with some practical recommendations and proposals for further research.

Patient selection

The patients for the studies in this thesis were derived from the CVT cohort of the University Medical Centre of Groningen (UMCG).

The UMCG-CVT is a single centre cohort. The use of a single centre cohort has advantages since the registered information is well controlled, but the drawback may be selection bias, which limits external validity. The characteristics of the cohort were comparable with other CVT cohorts described in the literature and this implies that the UMCG-CVT cohort consists of a representative group of CVT patients. However, patients with mild symptoms may be underrepresented in the published cohorts. Diagnosis modalities have improved and clinical awareness has increased during the last decades. Furthermore, the CVT cohorts are often collected in referral centres and this can result in selection of more severe patients. Setting up a prospective nationwide CVT registry could reduce this problem.

The UMCG-CVT cohort consisted of patients aged 15 years or older with a predominance of women between 20 and 40 years. CVT in children and in elderly patients may have another aetiology and outcome. CVT in children is thought to be more often secondary to local infections, while malignancy as risk factor is more common in elderly patients. The role of hormonal factors is likely to be less important in both children and patients older than 50 years. Further research in these specific subgroups of CVT patients is recommended.

Diagnosis of cerebral venous thrombosis

The clinical presentation of CVT varies widely. Currently, CVT is diagnosed or ruled out by neuroimaging of the cerebral veins. In patients with mild and common clinical symptoms, such as isolated headache, it can be difficult to assess the need for further investigation. In thrombosis of the deep veins of the legs (DVT), the Wells score is often used. This score consists of clinical variables, risk factors and the unlikelihood of an alternative diagnosis. It would be useful to develop such a score for CVT, which can help to measure the probability for CVT and the decision for further investigation.

Besides the Wells score, plasma levels of D-dimer are used in the diagnosis of DVT and pulmonary embolism (PE). Normal D-dimer levels have a high negative predicted value for DVT/PE. In contrast, D-dimer levels can be normal in CVT, especially in patients with mild symptoms. Other laboratory markers to assess the (un)likelihood for CVT may exist, but needs to be studied.

Prediction of outcome after CVT

The presented predictive outcome score in CVT may serve as a practical clinical tool for predicting outcome in CVT patients. The score is based on well-defined clinical variables and is relatively simple in use. The score accurately predicts good outcome. But only 4 out of 10 patients for whom poor outcome was predicted had a poor outcome and this limits its clinical use. Furthermore, the score is mainly applicable for mid- and long-term outcome. A score that could differentiate between poor and good outcome in the acute stage of this disorder to select CVT patients for high-risk treatment options, such as local thrombolysis or thrombectomy would be helpful.

Besides clinical variables, the use of laboratory markers in the acute stage can be studied. It would be of interest to measure coagulation and fibrinolytic markers in acute CVT patients and to investigate if these markers can predict high-risk patients for poor outcome.

Long-term outcome

CVT patients with a so-called 'good outcome', based on the modified Rankin scale (mRS) score, often have long-term sequelae, such as headache and concentration impairment. The clinician should be aware of these sequelae in daily clinical practice. The mRS is a widely used outcome scale in stroke research and mainly focuses on physical disability and functional independency. It may be less suitable to depict the more 'invisible' sequelae, impacting on daily life and employment status in the CVT patient.

The pathophysiological basis of the long-term sequelae requires further investigation. In patients with DVT, the post-thrombotic syndrome (PTS) is a well-known and frequent complication. The clinical characteristics of this syndrome are pain, oedema and skin alterations of the calf and are thought to be caused by venous insufficiency. It can be questioned if a CVT-PTS also exits due to insufficiency of the cerebral venous system. Patients often complain of headache after CVT. A hypothesis is that the headache after CVT may be caused by (intermittently) elevated intracranial pressure due to venous blood congestion. CVT may have disturbed the capacity of the cerebral venous blood flow return and small changes may lead to elevation of the intracranial pressure. Further investigation to test this hypothesis is engaging. Ocular sonography of the optic nerve sheath diameter may be a non-invasive test to measure intracranial pressure in CVT patients who complain of intermittent headache, since an increasing optic nerve sheath diameter is an indicator for elevated intracranial pressure. Serial measurements in patients with intermittent headache after CVT or comparing the optic nerve sheath diameter between patients with and without headache after CVT could gain insight into the pathophysiology of headache after CVT.

Site-specific thrombosis

The study comparing risk factors between CVT and DVT/PE in patients aged between 15 and 50 years underlines the role of age-dependent risk factors, but does not answer the 'key' question why a thrombus is more often located in the legs than in the brain. A possible explanation for the high incidence of DVT can be found in anatomical factors. The cerebral veins have no valves, in contrast to the deep veins of the lower legs. Valves may play a role in the development of DVT and induce stasis of blood, which may be enhanced by gravity and immobilization, and result in thrombus formation. Valves can, on the other hand, prevent reversal of blood flow, a mechanism that may be diminished with aging. Another explanation may be a site-specific difference in expression of anticoagulants and procoagulants of the local endothelium of the cerebral veins. The relatively high frequency of CVT in young women using oral contraceptives or being pregnant may be explained by an individual balance of coagulants that interact with hormonal factors. Genetic factors play a role in the balance of the coagulation and fibrinolytic system. Identification of new gene polymorphisms in CVT and studying the interaction with exogenous -especially female hormonal- factors may give more insight in the pathophysiology of CVT. In addition to the coagulation and fibrinolytic system, inflammatory processes are likely to play a role in the development of thrombosis, but little is known about this in CVT. In view of that, studying inflammatory markers, including cytokines and C-reactive protein, in CVT patients would be of interest to investigate the role of inflammation in the pathophysiology of CVT.

JAK2-V617F mutation and unusual site thrombosis

There is no association between the *Janus kinase 2* V617F (*JAK2*-V617F) mutation in CVT patients without a myeloproliferative disorder (MPD), in contrast to splanchnic vein thrombosis, which is, as CVT, an unusual site of thrombosis. This leads to the practical point that routine screening of the *JAK2*-V617F mutation in CVT patients without overt MPD is not recommended. The hypothesis of the association of the *JAK2*-V617F mutation with unusual site thrombosis irrespective of MPD has to be rejected. It is questionable whether thrombosis in unusual sites is associated with a unique factor or is the end of a thrombosis spectrum. It would be challenging to study other factors in rare site thrombosis to search for a unique factor which causes this thrombosis.

SAMENVATTING

Een trombose in de veneuze vaten van de hersenen, een cerebrale veneuze trombose (CVT), is een zeldzame oorzaak van een beroerte in vergelijking met een arteriële trombose. Naar schatting krijgen jaarlijks 3 tot 5 per miljoen mensen een CVT, voornamelijk vrouwen tussen 20 en 35 jaar. Het stellen van de diagnose van een CVT kan lastig zijn omdat de symptomen divers en vaak aspecifiek zijn. De meest voorkomende klacht is hoofdpijn. De hoofdpijn kan gepaard gaan met neurologische uitvalsverschijnselen of een epileptisch insult. Verwardheid en coma kunnen ook optreden. De diagnose wordt bevestigd met behulp van een CT- of MRI-scan van de hersenen met weergave van de veneuze vaten. Risicofactoren voor het krijgen van een CVT kunnen onderverdeeld worden in erfelijke stollingsafwijkingen en verworven factoren. Tot deze laatste groep behoren onder andere het gebruik van orale anticonceptie ('de pil'), zwangerschap, een locale infectie en kanker. Bij ongeveer 15 procent van de patiënten met een CVT wordt geen oorzaak gevonden. Dit suggereert dat er nog onbekende risicofactoren zijn. De behandeling van CVT bestaat veelal uit antistolling. De duur van de behandeling is afhankelijk van de oorzaak en varieert van 3 maanden tot levenslang. De prognose van CVT is over het algemeen gunstig. De laatste jaren is de kennis over CVT toegenomen, maar desondanks is er nog veel onduidelijk over de ontstaanswijze. Verder onderzoek zou kunnen leiden tot een beter inzicht in diagnose, behandeling en preventie.

De studies in dit proefschrift hebben als doel meer inzicht te krijgen in diverse klinische (hoofdstuk 3 tot en met 5) en pathofysiologische (hoofdstuk 6 en 7) aspecten van CVT. In de studies is gebruikt gemaakt van het register van CVT-patiënten uit het Universitair Medisch Centrum Groningen (UMCG) (hoofdstuk 2). Dit register bevat gegevens van 98 CVT-patiënten die tussen 1994 en 2009 zijn onderzocht.

Bij een zeldzame aandoening als CVT kan een prognostische score een hulpmiddel zijn bij het kiezen van een behandeling en bij de voorlichting aan de patiënt en familie. Hoofdstuk 3 beschrijft de studie naar een score om de uitkomst na een CVT te kunnen voorspellen. De score werd gebaseerd op 8 prognostische factoren voor een slechte uitkomst na een CVT. Deze gegevens waren afkomstig van de International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). De ISCVT is tot nu toe de grootste studie over CVT met in totaal 624 patiënten. Een slechte uitkomst na CVT was gedefinieerd als afhankelijkheid van zorg in het dagelijks leven of dood. Een goede uitkomst was gedefinieerd als onafhankelijkheid van zorg in het dagelijks leven. De ISCVT prognostische factoren voor een slechte uitkomst na een CVT waren: mannelijk geslacht, leeftijd ouder dan 37 jaar, mentale stoornissen, coma, hersenbloeding, infectie in het centrale zenuw stelsel, trombose in de diepe hersenvenen en kanker. De mate waarin een factor geassocieerd was met een slechte uitkomst in de ISCVT werd uitgedrukt in een gewogen index. De score van een individuele patiënt werd bepaald door de som van de gewogen indexen van de factoren die bij die patiënt aanwezig waren. Deze methode van prognosebepaling werd extern gevalideerd in 90 CVT-patiënten van het UMCG-cohort. Het optimale afkappunt werd gedefinieerd als de score met de maximale som van sensitiviteit en specificiteit. De prognostische score had een sensitiviteit van 88% en een specificiteit van 70%. De voorspellende waarde van goede uitkomst was 96% en de voorspellende waarde van slechte uitkomst was 39%. Uit de resultaten van dit extern validatie-onderzoek werd geconcludeerd dat de prognostische score nauwkeurig een goede uitkomst kon voorspellen, maar minder nauwkeurig was in het voorspellen van een slechte uitkomst na CVT.

De prognose van CVT is over het algemeen gunstig. De meerderheid van de patiënten herstelt goed en kan zonder zorg van anderen functioneren ('zorgonafhankelijkheid'). Uit de studie beschreven in hoofdstuk 4 bleek echter dat veel CVT-patiënten met een zogenaamde goede uitkomst minder 'zichtbare' (rest)klachten hebben. In een patiënt-controle onderzoek werd met behulp van een vragenlijst de frequentie van hoofdpijn, moeheid, depressie en concentratiestoornissen en de invloed hiervan op het dagelijks leven van 44 zorgonafhankelijke patiënten na CVT bepaald. Ongeveer de helft van deze patiënten had hinderlijke hoofdpijn en 75% had problemen met de concentratie. Depressieve klachten en moeheid kwamen bij 1 op de 3 patiënten voor. De patiënten hadden significant vaker klachten dan de controlegroep en de klachten hadden een negatieve invloed op het dagelijks functioneren en de werkhervatting. Het is belangrijk voor artsen en andere hulpverleners om kennis te hebben van en aandacht te besteden aan deze veelal weinig zichtbare restklachten na een CVT.

CVT is een zeldzame vorm van trombose en komt voornamelijk voor bij jonge vrouwen. Trombose in de diepe venen van het onderbeen (DVT) en/of een longembolie (PE) komt veel vaker voor, met name bij ouderen. Het is onbekend waarom een trombus vaker in de venen van de onderbenen voorkomt dan in het hoofd. Leeftijdsgerelateerde risicofactoren zouden een rol kunnen spelen. In de studie beschreven in hoofdstuk 5 werden de risicofactoren voor het krijgen van een trombose vergeleken tussen 79 CVT-patiënten en 173 DVT/PE-patiënten in de leeftijd van 15 tot en met 50 jaar. Er werden geen significante verschillen in trombofiele parameters tussen CVT-patiënten en DVT/PE-patiënten gevonden. De frequentie van sommige verworven risicofactoren was echter wel verschillend. CVT kwam relatief vaker voor bij vrouwen met orale anticonceptie en rondom de zwangerschap in vergelijking met DVT/PE. CVT was minder vaak het gevolg van een trauma, bedrust of een operatie in vergelijking met DVT/PE. Mogelijke verklaringen hiervoor zijn de afwezigheid van kleppen in de cerebrale venen, de invloed van de zwaartekracht of specifieke stollingsfactoren in de wand van de bloedvaten.

Er zijn veel factoren bekend die het risico op het krijgen van CVT verhogen. De studie in hoofdstuk 6 onderzocht of er een verhoogde stollingsneiging kon worden aangetoond bij CVT-patiënten. De stollingsneiging van 19 patiënten die een CVT hadden doorgemaakt en 19 controles werd geanalyseerd met een trombo-elastograaf. Een trombo-elastograaf meet in het bloed de tijd tot het ontstaan van een stolsel, de groei en maximale grootte van een stolsel. Er werden geen significante verschillen gevonden tussen de patiëntengroep en de controlegroep. Geconcludeerd werd dat in deze studie trombo-elastografie geen blijvende verhoogde stollingsneiging kon aantonen bij CVT-patiënten.

Hoofdstuk 7 beschrijft de studie waarin de associatie tussen een mutatie in het *Janus kinase 2* gen (*JAK2*-V617F mutatie) en CVT werd onderzocht. De *JAK2*-V617F mutatie komt frequent voor bij sommige myeloproliferatieve ziekten (MPZ). Trombose op verschillende locaties is een veel voorkomende complicatie bij MPZ-patiënten. Buikvenentrombose en CVT zijn beide zeldzame vormen van trombose. De *JAK2*-V617F mutatie komt vaak voor bij een trombose in de buikvenen en is zowel gevonden bij patiënten met een MPZ als bij patiënten zonder een MPZ. De studie onderzocht de associatie tussen de *JAK2*-V617F mutatie en CVT, onafhankelijk van MPZ. In de studie werd de aanwezigheid van de *JAK2*-V617F mutatie getest bij 59 CVT-patiënten van het UMCG-cohort. Van de 59 patiënten hadden 3 patiënten een MPZ, waarvan 2 de *JAK2*-V617F mutatie hadden. De mutatie werd niet gevonden bij 56 patiënten zonder een MPZ. De resultaten van deze studie en eerdere studies uit de medische literatuur suggereren dat de *JAK2*-V617F mutatie geassocieerd is met CVT in patiënten met een MPZ, maar niet in patiënten zonder een MPZ, dit in tegenstelling tot patiënten met een buikvenentrombose zonder een MPZ. Hieruit kan geconcludeerd worden dat standaard onderzoek naar *JAK2*-V617F mutatie bij CVT-patiënten zonder een MPZ niet noodzakelijk is.

De conclusies van de studies in dit proefschrift kunnen als volgt worden samengevat:

1. De ontwikkelde prognostische score kon nauwkeurig een goede uitkomst voorspellen, maar was minder nauwkeurig in het voorspellen van een slechte uitkomst na een CVT.
2. Patiënten met een zorgonafhankelijke uitkomst na een CVT hadden vaak last van minder zichtbare restklachten zoals hoofdpijn, concentratiestoornissen, moeheid en depressie en deze klachten hadden een negatieve invloed op het dagelijks functioneren.
3. Er konden geen verschillen worden aangetoond in trombofiele parameters tussen CVT-patiënten en DVT/PE-patiënten in de leeftijd van 15 tot en met 50 jaar, terwijl de frequentie van sommige verworven risicofactoren verschillend was: hormonale factoren waren meer geassocieerd met CVT, terwijl trauma, bedrust en een operatie meer geassocieerd waren met DVT/PE.
4. Trombo-elastografie kon geen verhoogde stollingsneiging aantonen bij patiënten die een CVT hadden doorgemaakt.
5. De *JAK2*-V617F mutatie was niet geassocieerd met CVT bij patiënten zonder een MPZ.

IN HERINNERING

Prof. dr. J. van der Meer

Jan

19-9-1950 14-1-2009

Jan van der Meer heeft een belangrijke rol gespeeld bij de totstandkoming van dit proefschrift. Tot aan zijn overlijden was hij als promotor nauw betrokken bij de studies. Veel ideeën en inzichten zijn op zijn kamer, tussen stapels papieren en boeken, ontstaan. De combinatie (vasculaire) neurologie-hematologie leverde levendige, verrassende en leerzame discussies op. Daarnaast kon hij op nauwkeurige wijze, meestal handmatig met een potloodje, de manuscripten corrigeren. Hij had een optimistische kijk op het onderzoek en moedigde aan vooral in eerste instantie 'hoog' in te zetten.

- J Thromb Haemost 5.5
- Thromb Haemost ~4.0
- Br J Haematol 4-5
- Blood 10-11

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CURRICULUM VITAE

Karen Koopman werd op 27 juni 1979 geboren te Hilversum. Na het voltooien van haar VWO opleiding aan het Alberdingk Thijm College te Hilversum in 1997, studeerde zij een jaar Bewegingswetenschappen aan de Vrije Universiteit van Amsterdam. In 1998 begon zij met haar studie Geneeskunde aan de Universiteit van Utrecht en behaalde haar Arts Examen op 11 december 2004.

In april 2005 begon zij aan de specialisatie tot neuroloog in het Universitair Medisch Centrum Groningen (voormalig opleider prof. dr. J.H.A. De Keyser, huidige opleider prof. dr. H.P.H. Kremer). Vanaf april 2007 combineerde zij de klinische opleiding met onderzoek naar cerebrale veneuze trombose. De verwachte einddatum van haar specialisatie tot neuroloog is april 2011.